2025 VIRBAC Product Guide

TABLE OF CONTENTS

A LEGACY OF CARE, A FUTURE OF INNOVATION

Veterinarian Pierre-Richard Dick founded Virbac in 1968 to bridge the gaps in animal health care and develop products tailored to the needs of veterinarians, producers and pet owners.

Today, Virbac continues its legacy as a global leader in animal health, driving innovation to meet the evolving needs of animal caregivers. By combining animal health professional insights with the latest technological advances, we create practical solutions and products held to the highest standards.

For over 50 years, we have built trusted relationships with veterinarians like you who are dedicated to animal care and advancing the future of animal health together.

PROTECTING LIFE | CARING FOR COMPANION ANIMALS
PROMOTING FARM ANIMALS' HEALTH | INNOVATING TOMORROW

Product List....4-5
Highlighting Livestock Health....6
Highlighting Mobility....8
Highlighting At-Home Dental Care....10
Highlighting Dermatology....12
Highlighting Pet Nutrition....14
Antibiotics....16
Behavior....18
Dental Health....20
Dermatology....24
Heartworm and Parasiticides....29
In-Clinic Use....34
Mobility....36
Pet Nutrition....37
Supplements....42
Livestock Health....44
Product Inserts/Disclosures....48

If you have any questions regarding these products, please contact the Virbac Product Safety & Consulting Team at 1-800-338-3659 or your local Virbac representative.

PRODUCT LISTING

ANTIBIOTICS PAGE 16-17

AYRADIA™ (metronidazole oral suspension)

BIOMOX® (amoxicillin tablets)

CLINTABS® (clindamycin hydrochloride tablets)

RILEXINE® (cephalexin tablets) Chewable Tablets

BEHAVIOR PAGES 18-19

ANXITANE® (L-Theanine) Chewable Tablets

CLOMICALM® (clomipramine hydrochloride) tablets

ZENIDOG® Pheromone Products

ZENIFEL™ Pheromone Products

DENTAL HEALTH PAGES 20-23

C.E.T. AQUADENT® FR3SH® Dental Solution

C.E.T.® Cat Toothbrush w/ 0.4 oz (12 g) Trial-Size Packet

C.E.T.® Dual-Ended Toothbrush

C.E.T.® Enzymatic Oral Hygiene Chews for Dogs

C.E.T.® Enzymatic Toothpaste

C.E.T.® Enzymatic Toothpaste - Trial-Size Packets Dispenser

C.E.T.® Fingerbrush w/ 0.4 oz (12 g) Trial-Size Packet

C.E.T.® HEXTRA® Premium Oral Hygiene Chews for Dogs

C.E.T.® INTELLIDENT® Cat Bites

C.E.T.® Mini-Toothbrush w/ 0.4 oz (12 g) Trial-Size Packet

C.E.T.® Oral Hygiene Kits

C.E.T.® Pet Toothbrush

C.E.T.® Pet Toothbrush Bulk Dispenser

C.E.T.® VEGGIEDENT® Flex Tartar Control Chews for Dogs

C.E.T.® VEGGIEDENT® FR3SH® Tartar Control Chews for Dogs

C.E.T.® VEGGIEDENT® Zen Tartar Control Chews for Dogs

DERMATOLOGY PAGES 24-28

ALLERDERM® Foaming Cleanser

ALLERDERM OMEGADERM® Essential Fatty Acids Supplement

ALLERGROOM® Shampoo

ALLERMYL® (Piroctone Olamine) Medicated Shampoo

CYCLAVANCE® (cyclosporine oral solution) USP MODIFIED

EASOTIC® (hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension for Dogs

EPIOTIC® *Advanced* Ear Cleanser

EPI-SOOTHE® Cream Rinse

EPI-SOOTHE® Shampoo

GENESIS® Topical Spray (solution of 0.015% triamcinolone acetonide)

ITRAFUNGOL® (itraconazole oral solution)

KERATOLUX® (Piroctone Olamine) Medicated Shampoo

KETOCHLOR® (Chlorhexidine Gluconate, Ketoconazole) Medicated Shampoo

OTOMITE PLUS® Ear Miticide

HEARTWORM & PARASITICIDES PAGES 29-33

EFFIPRO® PLUS Topical Solution for Cats

EFFIPRO® PLUS Topical Solution for Dogs

EFFITIX® PLUS Topical Solution for Dogs

IVERHART MAX® Chew (ivermectin/pyrantel pamoate/praziquantel)

IVERHART PLUS® (ivermectin/pyrantel) *Flavored Chewables*

KNOCKOUT® Brand Products

PARASEDGE® Multi for Dogs (imidacloprid + moxidectin) Topical Solution

PARASEDGE® Multi for Cats (imidacloprid + moxidectin) Topical Solution

SENERGY® (selamectin) Topical Parasiticide for Dogs and Cats

VIRBANTEL® (pyrantel pamoate/praziquantel) Flavored Chewables

IN-CLINIC USE PAGES 34-35

EUTHASOL® (pentobarbital sodium and phenytoin sodium) Euthanasia Solution

STELFONTA® (tigilanol tiglate injection)

SUPRELORIN® F (deslorelin acetate) Implant

ZOLETIL® (tiletamine and zolazepam for injection)

MOBILITY PAGE 36

MOVODYL® Chewable Tablets (carprofen)

MOVOFLEX® Advanced Soft Chews

URSOLYX™ Soft Chews

PET NUTRITION PAGES 37-41

Coldwater Culinary™ Canine Diet

Healthy Gourmet™ Pet Foods

Healthy Rewards Canine Low Fat Treats

NutriCare™ Canine Diets

SensiSnacks™ Hydrolyzed Low Fat Canine Treats

VetBasics™ Dog Foods

VETERINARY HPM® Spay & Neuter Diets

SUPPLEMENTS PAGE 42

NEPHRODYL™ Synbiotic Capsules

REBOUND® Recuperation Formula

COMMITTED TO GROWTH

LIVESTOCK HEALTH PAGES 44-47

BOVIGEN™ Platinum Vaccine Line

Tenotryl™ (enrofloxacin) injectable solution

Tulissin® 100 (tulathromycin injection) injectable solution

Tulissin® 25 (tulathromycin injection) injectable solution








URSOLYX™ SOFT CHEWS

SCIENCE WITH MUSCLE

QUALITY SEAL nasc NATIONAL ANIMAL SUPPLEMENT COUNCIL

MADE IN USA INCLUDING U.S. & GLOBALLY SOURCED MATERIALS

everyday CARE

PIONEERING SCIENCE

supporting muscle health so dogs can be dogs again

Demonstrated safety and efficacy[1]

Ursolic acid derived from sage extract

1 chew per day

Proprietary coating for optimal bioavailability[1]

60 Soft chews per jar

High acceptability[1] for easy administration

Scientifically proven to enhance your canine patients' muscle health in just 8 weeks[1] — redefine what's possible.

This first-in-its-class muscle support features ursolic acid, which targets mRNA expression in skeletal muscle. URSOLYX™ Soft Chews leverage this compound's demonstrated efficacy[1] to promote muscle function and strength in aging, active or recuperating canine patients.

Reference 1. Ebert SM, Nicolas CS, Schreiber P, et al. Ursolic acid induces beneficial changes in skeletal muscle mRNA expression and increases exercise participation and performance in dogs with age-related muscle atrophy. *Animals (Basel).* 2024;14(2):186. doi:10.3390/ani14020186

SCAN TO LEARN MORE

Virbac Shaping the future of animal health

C.E.T.® HOME DENTAL CARE | #1 VETERINARIAN RECOMMENDED BRAND[1]

Award-winning[1] dental care

The Keys to Better Dental Health for Your Pet:

Routine Professional Cleaning + Daily At-Home Dental Care

High quality

Science based

Easy to administer

3 Easy Steps to Dental Wellness

BRUSH

Enzymatic toothpastes & toothbrushes for every pet

BITE

Tasty canine chews & feline bites help reduce plaque & tartar buildup

BOWL

Dental solution controls plaque for cleaner teeth, healthier gums & fresher breath

Take our Dental Authority Certification Program at **cetambassador.virbac.com**.

everyday CARE

Reference: 1. 2023 top recommended veterinary products™. dvm360. Accessed February 18, 2025. https://www.dvm360.com/pet-products-guide

Virbac

Block out their ear discomfort and keep them comfortable.

Otitis externa hurts. Provide fast **relief now**.

As early as day 2:
Statistically significant differences (vs. CLARO®) in improvement of discharge, stenosis and odor[1]

See results from post-marketing study.

easOtic®
(hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension For Dogs

Help more dogs find **fast relief** from signs of otitis externa.

Important Safety Information
EASOTIC® (hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension for Dogs: For otic (ear) use in dogs only. Do not use in dogs with known tympanic membrane (ear drum) perforation. Immediately discontinue use of EASOTIC Otic Suspension if hearing loss or signs of vestibular dysfunction are observed during treatment. See full prescribing information on page XX.

Support their ear health for the **long term** with routine cleansing.

Help more dog owners **easily maintain** their dogs' ear health.

Ideal for dogs prone to otitis externa, including:

- Dogs with allergies
- Dogs that swim or tend to get wet often
- Dogs with floppy ears

EpiOtic® Advanced
Powerful and gentle ear cleanser

VIRBAC DERMATOLOGY SOLUTIONS
For comprehensive comfort

Virbac Shaping the future of animal health

Reference: 1. von Simson C, Poincelot L, Jasmin P, Griffin J. Comparison of the efficacy of a gentamicin, miconazole and hydrocortisone aceponate formulation and a florfenicol, terbinafine and mometasone furoate formulation in the treatment of canine otitis externa with a focus on onset of action. Abstract presented at: World Congress of Veterinary Dermatology; July 25-29, 2024; Boston, MA.

It's easier to prevent weight gain than it is to treat obesity.

2021 AAHA Nutrition and Weight Management Guidelines

Proactive Weight Management with VETERINARY HPM® Spay & Neuter Diets

VETERINARY HPM® Spay & Neuter Diets offer a proactive weight management solution for your clinic, starting with custom nutrition designed to help prevent weight gain in altered pets. This unique diet is tailored to address metabolic changes to support long-term well-being. Through a unique High-Protein, High-Fiber and Reduced-Carb formulation, this diet helps:[1,2,3,4,5]

- **Support metabolism** with 84% animal protein and balanced nutrients for energy regulation.
- **Manage weight & appetite** with protein and fiber for satiety and optimal weight.
- **Maintain lean muscle** with high-quality protein.
- **Aid digestion** with prebiotics and fiber for gut balance.
- **Support growth** with consistent energy, proteins and minerals.

With 80–90% of pets in the U.S. spayed or neutered,[6] it's clear that this isn't a niche issue—it's the norm. Spaying and neutering is the #1 risk factor for obesity in pets,[7] making proactive nutrition more important than ever.

When to Have Proactive Nutrition Conversations:

- ☑ New puppy or kitten visits
- ☑ Spay/neuter pre-op appointments
- ☑ New rescue or new pet appointments
- ☑ Annual exams, especially with noted weight gain
- ☑ New pet exams for adult dogs or cats previously spayed/neutered

VET EXCLUSIVE. PET FIRST.
EASY TO SUBSCRIBE + SAVE. iVet.com™

VETERINARY HPM®

1. Leriche I et al, Virbac poster presentation ASAS 2015
2. Martin LJ, Siliart B, Lutz TA, Biourge V, Nguyen P, Dumon HJ. Postprandial response of plasma insulin, amylin and acylated ghrelin to various test meals in lean and obese cats. *Br J Nutr*. 2010 Jun;103(11):1610-9. doi: 10.1017/S000711450999359X. Epub 2010 Jan 26. PMID: 20100379.
3. Gerstein DE, Woodward-Lopez G, Evans AE, Kelsey K, Drewnowski A. Clarifying concepts about macronutrients' effects on satiation and satiety. *J Am Diet Assoc*. 2004 Jul;104(7):1151-3. doi: 10.1016/j.jada.2004.04.027. PMID: 15215775.
4. Vester BM et al. In utero and postnatal exposure to a high protein or high carbohydrate diet leads to differences in adipose tissue mRNA expression and blood metabolites in kittens. *Br J Nutr* 2009; 102:1136-1144.
5. Reduced carbohydrates in relation to VetBasics™ and other retail diets. Source of file at Virbac.
6. Association for Pet Obesity Prevention, the Annual Survey
7. WSAVA Nutritional Assessment for Dogs and Cats

ANTIBIOTICS

AYRADIA™ (metronidazole oral suspension) for dogs

- The first FDA-approved liquid metronidazole for veterinary use
- Chicken-flavored liquid for easy dosing
- Three-year shelf life prior to opening
- Accurate dosing for dogs and puppies of all weights
- Proven effective against *Giardia duodenalis*

Available in:
30 mL SKU 13100
100 mL SKU 13101

Important Safety Information
AYRADIA™ (metronidazole oral suspension): Not for use in humans. Avoid contact with skin and wash hands after use. In dogs, neurologic effects have been associated with AYRADIA oral suspension use at high doses. Use with caution in dogs with hepatic dysfunction. The safe use of this drug in dogs intended for breeding purposes and in pregnant or lactating bitches has not been evaluated.

See package insert at the end of the Product Guide for full product information.

BIOMOX® (amoxicillin tablets)

- Broad-spectrum antibiotic for veterinary use to provide bactericidal activity against a wide range of common pathogens
- Indicated for the treatment of soft tissue infections such as:
  - Abscesses
  - Wounds
  - Lacerations
- Can be administered with or without food

Available in scored, flavored chewable tablets:
50 mg (500 tablets) SKU 92505
100 mg (500 tablets) SKU 92105
200 mg (500 tablets) SKU 92205

Important Safety Information
BIOMOX® (amoxicillin tablets): For use in dogs only. Contraindicated in animals with a history of an allergic reaction to penicillin. If an allergic reaction occurs, epinephrine and/or steroids should be administered. Do not use in pregnant or breeding animals.

See package insert at the end of the Product Guide for full product information.

CLINTABS® (clindamycin hydrochloride tablets)

- First tier antibiotic for skin infections[1]
- Easy-to-swallow tablet form
- A bacteriostatic antibiotic indicated for the treatment of susceptible dental and skin infections (wounds and abscesses) and osteomyelitis for dogs only

Available in:
25 mg (400 tablets) SKU 902540
75 mg (200 tablets) SKU 907520
150 mg (100 tablets) SKU 915010

Important Safety Information
CLINTABS® (clindamycin hydrochloride tablets): Keep out of reach of children. Not for human use. Contraindicated in animals with a history of hypersensitivity to clindamycin or lincomycin. Do not use in rabbits, hamsters, guinea pigs, horses, chinchillas or ruminating animals. Use with caution in patients with very severe kidney or liver disease and in animals receiving neuromuscular blocking agents such as succinylcholine. Safety in pregnant females or breeding males has not been established. Monitor blood work in animals on either high dose or prolonged therapy. Side effects occasionally observed include vomiting and diarrhea.

See package insert at the end of the Product Guide for full product information.

RILEXINE® (cephalexin tablets) Chewable Tablets

The first and only FDA veterinary-approved cephalexin indicated for the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *S. pseudintermedius*.

- First tier antibiotic for skin infections[1]
- Palatable formulation that dogs readily accept
- Tablets available in three sizes and scored for precise dosing

Available in scored, flavored chewable tablets:
150 mg (100 tablets) SKU 07620
300 mg (100 tablets) SKU 07630
600 mg (100 tablets) SKU 07640

Important Safety Information
RILEXINE® (cephalexin tablets) Chewable Tablets: For oral use in dogs only. People with sensitivities to penicillins or cephalosporins should avoid contact with this product. RILEXINE Chewable Tablets are very palatable for pets and should be stored in a secure location where pets cannot access them. Do not give to dogs with known allergy to penicillins or cephalosporins. Safety in pregnant females or breeding males has not been established. The most common adverse reactions in dogs include diarrhea, vomiting, anorexia and lethargy.

See package insert at the end of the Product Guide for full product information.

1. Hillier, A., Lloyd, D. H., Weese, J. S., Blondeau, J. M., Boothe, D., Breitschwerdt, E., Guardabassi, L., Papich, M. G., Rankin, S., Turnidge, J. D., & Sykes, J. E. (2014). Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases).Veterinary Dermatology, 25(3), 163-e43. https://doi.org/10.1111/vde.12118

ANXITANE® (L-Theanine) Chewable Tablets

- Supplement for dogs and cats for anxious behavior
- Promotes relaxation in cats and dogs exhibiting nervousness, responding to environmentally induced stress or are anxious without causing drowsiness or sedation
- Containing a synthetic form of L-Theanine, an amino acid naturally found in green tea leaves
- ANXITANE Chewable Tablets are a palatable option both cats and dogs will enjoy
- Not intended for use in animals with severe phobias, separation anxiety or in animals with a known history of aggression

Available in 30-count box:

Small (all cats and dogs < 22lbs); 50 mg tablets
SKU 10432

Medium/Large (dogs > 22 lbs); 100 mg tablets
SKU 10435

CLOMICALM® (clomipramine hydrochloride) tablets

- Effective treatment for canine separation anxiety as part of a behavioral management program for use in dogs greater than 6 months of age
- Clomipramine hydrochloride, the active ingredient in CLOMICALM tablets, binds to the serotonin uptake receptor and prevents the removal of excess serotonin; this increases positive emotional neural signaling in the brain
- Artificial beef flavoring
- Scored tablet

Available in:
5 mg (30 tablets) SKU 10520
20 mg (30 tablets) SKU 10522
80 mg (30 tablets) SKU 10523

Important Safety Information
CLOMICALM® (clomipramine hydrochloride) tablets: For use in dogs only. Keep out of reach of children. In children, accidental ingestion should be regarded as serious. Do not administer to dogs with hypersensitivity to clomipramine or other tricyclic antidepressants. CLOMICALM tablets should not be used in: 1) male breeding dogs; 2) combination or within 14 days before or after treatment with a monoamine oxidase inhibitor; 3) dogs with a history of seizures or concomitantly with drugs which lower the seizure threshold. CLOMICALM tablets are not recommended for other behavior problems such as aggression. Effectiveness and clinical safety for long-term use (i.e., for >12 weeks) has not been evaluated. To reduce the incidence of vomiting that may be experienced by some dogs, CLOMICALM tablets may be given with a small amount of food.

See package insert at the end of the Product Guide for full product information.

NEW FOR CATS ZENIFEL™ Gel Diffuser

- Contains F3 fraction of feline facial pheromone analogues and Nepeta cataria (catnip) extract.
- Signs of stress reduced up to 80%[2]
- Electric free (no need for an electrical outlet)
- Lasts up to 2 months: 2 times longer than the market leader[1,2]
- Slow-release technology for maximum shelf life
- Covers up to 750 square feet

Available in:
8.1 oz SKU 10300

ZENIDOG® Gel Diffuser

- Contains analogue of canine appeasing pheromone
- Signs of stress reduced up to 89%[4]
- Electric free (no need for an electrical outlet)
- Lasts up to 2 months: 2 times longer than the market leader[2,4]
- Slow-release technology for maximum shelf life
- Covers up to 750 square feet

Available in:
8.1 oz SKU 10518

NEW FOR CATS ZENIFEL™ Spray

- Contains F3 fraction of feline facial pheromone analogues and Nepeta cataria (catnip) extract.
- Offers rapid, short-term calming effect[2]
- Easy-to-use, delivering a minimum of 400 sprays
- More effective than the market leader[3]
- Odorless

Available in:
60 mL SKU 10301

ZENIDOG® Long-Acting Collar

- Contains analogue of canine appeasing pheromone
- Signs of stress reduced up to 89%[4]
- Lasts up to 3 months: 3 times longer than the market leader[4]
- Can be used with flea and tick collars, with no change in effectiveness[2]
- Odorless

Available in:
18.3 in. collar (puppies/small dogs up to 22 lbs)
SKU 10512

29.5 in. collar (medium/large dogs 22.1-110 lbs)
SKU 10513

1. Espuña G, Nicolas CS, Girardin A, Fatjó J, Bowen J, Monginoux P, Rème CA. A long-lasting gel-based diffuser of feline pheromone can help reduce undesirable behaviors in cats at home: comparison with an electric diffuser. *Front Vet Sci.* 2024;11:1445108. doi:10.3389/fvets.2024.1445108:39268519; PMC11390375

2. Data on file. Virbac Corporation.

3. Bernachon N, Beata C, Crastes NC, et al. Response to acute stress in domestic cats using synthetic analogues of natural appeasing pheromones with nepeta cateria extract rich in nepetalactone: a double-blinded, randomized, positive controlled cross-over study. *J App Res Vet Med.* 2015;13(2):125-134.

4. Nicolas CS, Espuña G, Girardin A, Fatjó J, Bowen J, Monginoux P. Owner-perception of the effects of two long-lasting dog-appeasing pheromone analog devices on situational stress in dogs. *Animals (Basel).* 2022;12(1):122. doi:10.3390/ani12010122

C.E.T.® VEGGIEDENT® DENTAL CHEWS

C.E.T.® VEGGIEDENT® FR3SH® Tartar Control Chews for Dog

- Multifunctional dental chew to support digestive health
- Made with FR3SH® Technology that delivers fresh breath and more
- Just one chew per day reduces tartar and plaque
- Highly palatable
- Unique Z-shape allows the chew to reach front to back
- Supports at-home dental care between professional cleanings

Available in 30 chews per bag:
Extra Small: < 11 lbs SKU 90055
Small: 11-22 lbs SKU 90056
Medium: 22-66 lbs SKU 90057
Large: > 66 lbs SKU 90058

C.E.T.® VEGGIEDENT® Flex Tartar Control Chews for Dogs

- Multifunctional dental chew to support joint health
- Made with FR3SH® Technology that delivers fresh breath and more
- Formulated with BIOVAFLEX® eggshell membrane
- Just one chew per day reduces tartar and plaque
- Highly palatable
- Unique Z-shape allows the chew to reach front to back
- Supports at-home dental care between professional cleanings

Available in 30 chews per bag:
Extra Small: < 11 lbs SKU 90085
Small: 11-22 lbs SKU 90086
Medium: 22-66 lbs SKU 90087
Large: > 66 lbs SKU 90088

C.E.T.® VEGGIEDENT® Zen Tartar Control Chews for Dogs

- Multifunctional dental chew to support mental well-being
- Made with FR3SH® Technology that delivers fresh breath and more
- Formulated with L-Theanine
- Just one chew per day reduces tartar and plaque
- Highly palatable
- Unique Z-shape allows the chew to reach front to back
- Supports at-home dental care between professional cleanings

Available in 30 chews per bag:
Extra Small: < 11 lbs SKU 90075
Small: 11-22 lbs SKU 90076
Medium: 22-66 lbs SKU 90077
Large: > 66 lbs SKU 90078

DENTAL HEALTH

CHEWS AND SOLUTIONS

C.E.T.® INTELLIDENT® Cat Bites

- Freshens breath by working with cat's natural chewing action to help reduce plaque and tartar
- Results shown with only 3 bites per day
- Crunchy porous texture to provide an effective clean

Available in:
90 bites per bag
SKU 90700

C.E.T.® Enzymatic Oral Hygiene Chews for Dogs

- Features an exclusive Dual-Enzyme System, plus an abrasive texture that works with the dog's chewing action to remove tartar and provide plaque control
- Contains single layer beef hide for a natural abrasive cleansing action
- Appealing poultry flavor

Available in:
Extra Small: < 11 lbs, 8.4 oz SKU 90601
Small: 11-25 lbs, 8.5 oz SKU 90603
Medium: 26-50 lbs, 12.8 oz SKU 90605
Large: > 50 lbs, 1.13 lbs SKU 90607

C.E.T. AQUADENT® FR3SH® Dental Solution

- Daily water additive to fight the source of bad breath
- Supports healthy teeth and gums by controlling plaque in dogs and cats
- Combination of 3 natural ingredients:
  - Erythritol: a natural sweetener, has a freshening effect in mouth
  - Inulin: a natural prebiotic to help control bad breath
  - Pomegranate Extract: a natural antioxidant
- For use in dogs and cats

Available in:
8.45 fl oz (250 mL) SKU 90508
16.9 fl oz (500 mL) SKU 90516

C.E.T.® HEXTra® Premium Oral Hygiene Chews for Dogs

- Natural rawhide coated with solution of chlorhexidine that helps reduce plaque and tartar
- Contains single layer beef hide for a natural abrasive cleansing action
- Appealing poultry flavor
- Chew size and thickness may vary

Available in:
Extra Small: < 11 lbs, 8.4 oz SKU 90612
Small: 11-25 lbs, 8.5 oz SKU 90614
Medium: 26-50 lbs, 12.8 oz SKU 90616
Large: > 50 lbs, 1.13 lbs SKU 90618

For more information, call 1-800-338-3659 or visit vet-us.virbac.com.

DENTAL HEALTH

TOOTHPASTES, TOOTHBRUSHES AND KITS

C.E.T.® HOME DENTAL CARE | #1 VETERINARIAN RECOMMENDED BRAND®

C.E.T.® Enzymatic Toothpaste

- Formulated using an enzyme system to reduce plaque, freshen breath and ensure a clean mouth
- No foaming agents, so it is safe for pets to swallow
- Available in 5 flavors: Beef, Malt, Poultry, Seafood, Vanilla-Mint
- For use in dogs and cats

Available in:
2.5 oz (70 g) tube – Beef SKU CET201
2.5 oz (70 g) tube – Malt SKU CET102
2.5 oz (70 g) tube – Poultry SKU CET101
2.5 oz (70 g) tube – Seafood SKU CET202
2.5 oz (70 g) tube – Vanilla-Mint SKU CET103
Poultry flavor is also available in 0.4 oz (12 g) trial-size packets in a 25-count dispenser SKU CET002

C.E.T.® Pet Toothbrush

- Soft bristles for pet comfort and acceptance
- Small end with reverse angle allows for easy application
- Individually packaged, assorted colors
- Available individually or in a 24 ct. dispenser

C.E.T. Pet Toothbrush SKU CET304
C.E.T. Pet Toothbrush Bulk Dispenser SKU CET350

C.E.T.® Dual-Ended Toothbrush

- Long handle with reverse angle allows for easy application
- Tapered end conforms to pet's mouth and teeth
- Dual-ended for large and small tooth surfaces
- Soft bristles assure a gentle, well-tolerated application
- Individually packaged, assorted colors

C.E.T. Dual-Ended Toothbrush SKU CET305

C.E.T.® Mini-Toothbrush

- Soft bristles for pet comfort and acceptance
- Small end and fingertip design allow for easy access
- Also contains a 0.4 oz (12 g) trial-size packet of poultry-flavored toothpaste

C.E.T. Mini-Toothbrush w/0.4 oz Trial Packet SKU CET302

C.E.T.® Cat Toothbrush

- Soft, gentle, easy to use
- Long, soft bristles with a pointed tuft
- Unique shape is designed for the limited confines of the feline mouth
- Also contains a 0.4 oz (12 g) trial-size packet of poultry-flavored toothpaste

C.E.T. Cat Toothbrush w/0.4 oz Trial Packet SKU CET303

C.E.T.® Fingerbrush

- Ideal beginner toothbrush to help acquaint dogs, cats and their owners with the toothbrushing experience
- Convenient design and excellent pet acceptance
- Made of durable, dishwasher-safe material
- Helps remove plaque from tooth surface
- Massages and strengthens gums
- Also contains a 0.4 oz (12 g) trial-size packet of poultry-flavored toothpaste

C.E.T. Fingerbrush w/0.4 oz Trial Packet SKU CET301

C.E.T.® Oral Hygiene Kit for Cats

- Contains:
  - C.E.T.® Enzymatic Toothpaste
  - C.E.T.® Fingerbrush
  - C.E.T.® Cat Toothbrush

Oral Hygiene Kit for Cats, Seafood-flavor Toothpaste 2.5 oz (70 g) SKU CET402

C.E.T.® Cat Toothbrush with 0.4 oz (12 g) Trial Packet

- Contains:
  - C.E.T.® Cat Toothbrush
  - C.E.T.® Enzymatic Toothpaste

Cat Toothbrush with 0.4 oz (12 g) Trial Packet SKU CET303

C.E.T.® Fingerbrush with 0.4 oz (12 g) Trial Packet

- Contains:
  - C.E.T.® Fingerbrush
  - C.E.T.® Enzymatic Toothpaste

Fingerbrush with 0.4 oz (12 g) Trial Packet SKU CET301

C.E.T.® Oral Hygiene Kit for Dogs

- Contains:
  - C.E.T.® Enzymatic Toothpaste
  - C.E.T.® Fingerbrush
  - C.E.T.® Dual-Ended Toothbrush

Oral Hygiene Kit for Dogs, Poultry-flavor Toothpaste 2.5 oz (70 g) SKU CET401

C.E.T.® Mini-Toothbrush with 0.4 oz (12 g) Trial Packet

- Contains:
  - C.E.T.® Mini-Toothbrush
  - C.E.T.® Enzymatic Toothpaste

Mini-Toothbrush with 0.4 oz (12 g) Trial Packet SKU CET302

EASOTIC® (hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension for Dogs

Relieve otitis signs now

- Proven fast relief of pain and discomfort[1]
- Unique anti-inflammatory, hydrocortisone aceponate (HCA) is a next-generation di-ester steroid with a favorable benefit/risk ratio[2]
- Shown to provide effective treatment of otitis externa with 5 once-daily doses
- Features an ergonomically designed applicator for easy application
- For use in dogs only

Available in:
10 mL (10 doses) SKU 09420

Important Safety Information
EASOTIC® (hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension for Dogs: For otic (ear) use in dogs only. Humans with known or suspected hypersensitivity to hydrocortisone, aminoglycoside antibiotics or azole antifungals should not handle this product. Contraindicated in dogs with known or suspected hypersensitivity to corticosteroids, imidazole antifungals or amino-glycoside antibiotics. Do not use in dogs with known tympanic membrane (ear drum) perforation. The safe use of EASOTIC Otic Suspension in dogs used for breeding purposes has not been evaluated. Do not administer orally.

See package insert at the end of the Product Guide for full product information.

1. von Simson C, Poincelot L, Jasmin P, Griffin J. Comparison of the efficacy of a gentamicin, miconazole and hydrocortisone aceponate formulation and a florfenicol, terbinafine and mometasone furoate formulation in the treatment of canine otitis externa with a focus on onset of action. Abstract presented at: World Congress of Veterinary Dermatology; July 25-29, 2024; Boston, MA.
2. Wohlrab, J., Beck, G. M., Neubert, R. H. H., Sischka, U., & Kreft, B. (2010). Hydrocortisone aceponate activity and benefit/riskratio in relation to reference topical glucocorticoids. Skin Pharmacology and Physiology, 23(4), 177–182. https://doi.org/10.1159/000288164

EPIOTIC® *Advanced* Ear Cleanser

The powerful and gentle cleanser for cats and dogs, particularly those prone to otitis externa.

- Allergic/atopic animals
- Frequent swimmers
- Those with floppy ear anatomy, creating an environment that can encourage microbial overgrowth

- Non-stinging, non-irritating, yet powerful cleansing
- Safe to be used daily or 2-3 times per week
- Limits the bonding of microorganisms to the ear canal surface
- Provides a drying effect
- Keeps ears smelling fresh

Available in:
4 fl oz (118 mL) SKU 003104
8 fl oz (237 mL) SKU 003108

OTOMITE PLUS® Ear Miticide

- For treatment of ear mites in dogs, cats, puppies and kittens over 12 weeks of age
- Soothing olive oil base facilitates the dispersal and penetration
- Synergistic active ingredients:
  - 0.15% Pyrethrins
  - 1.50% Piperonyl Butoxide
  - 0.48% n-Octyl bicycloheptene

Available in:
0.5 fl oz (14.7 mL) SKU 601712

GENESIS® Topical Spray (solution of 0.015% triamcinolone acetonide)

- Proven relief for itchy skin
- Controls pruritus associated with allergic dermatitis in dogs
- Powerful topical anti-inflammatory action

Available in:
8 fl oz (237 mL) bottle with sprayer SKU 410508
16 fl oz (478 mL) bottle with sprayer SKU 410500

Important Safety Information
GENESIS® Topical Spray (solution of 0.015% triamcinolone acetonide): For use on dogs only. Wear gloves when applying the product. The use of this product on dogs less than 8 pounds, less than one year of age, breeding, pregnant or lactating has not been evaluated. Adverse events of polyuria and polyphagia have been reported in <6% of dogs receiving treatment.

See package insert at the end of the Product Guide for full product information.

CYCLAVANCE® (cyclosporine oral solution) USP MODIFIED 100 mg/mL

- The effective cyclosporine you know and trust— in liquid form
- Indicated for the control of atopic dermatitis in dogs weighing at least 4 lbs (1.8 kgs)
- Convenient and easy dosing to help promote compliance
- Precise dosing — CYCLAVANCE oral solution eliminates the inefficiencies of dosing with capsules

Available in two vial presentations:
15 mL SKU 20301
50 mL SKU 20303

Important Safety Information
CYCLAVANCE® (cyclosporine oral solution) USP MODIFIED: For use in dogs only. Wear gloves during and wash hands after administration. Gastrointestinal problems and gingival hyperplasia may occur at the initial recommended dose of CYCLAVANCE oral solution. CYCLAVANCE oral solution should be used with caution: 1) in cases with diabetes mellitus as it may cause elevated levels of serum glucose; 2) in dogs with renal insufficiency since the effect of cyclosporine use on dogs with compromised renal function has not been studied; 3) in simultaneous administration with drugs that suppress the P-450 enzyme system, such as azoles (e.g., ketoconazole), that may lead to increased plasma levels of cyclosporine. Killed vaccines are recommended for dogs receiving CYCLAVANCE oral solution because the impact of cyclosporine on the immune response to modified live vaccines has not been evaluated.

See package insert at end of the Product Guide for full product information.

ITRAFUNGOL®
(itraconazole oral solution) 10 mg/mL

The only oral FDA-approved treatment for feline dermatophytosis (ringworm) for easy administration

- Cherry-caramel liquid formulation for easy dosing
- Can be dosed with or without food
- In a clinical study, 80 cats infected with Microsporum canis were treated with either placebo or ITRAFUNGOL oral solution, pulse-dosed (5 mg/kg/day) over alternate weeks for three treatments and followed by a 4-week follow-up period. No topical therapy was used. In the group treated with ITRAFUNGOL oral solution[1]:
  - Clinical cure occurred well in advance of mycological cure
  - 90% had at least one negative fungal culture by the end of the study
  - 98% had complete resolution of all clinical lesions, compared to 15% of untreated cats by the end of the study
- Shelf life is two years unopened or five weeks once opened

Available in:
52 mL bottle SKU 11605
One bottle provides treatment course for a 10 lb cat

Important Safety Information
ITRAFUNGOL® (itraconazole oral solution): For use in cats only. Wash hands and exposed skin after use. Do not administer to cats with hypersensitivity to itraconazole. ITRAFUNGOL oral solution has not been shown to be safe in pregnant cats and should only be used in pregnant or lactating cats when the benefits outweigh the potential risks. Administer orally using the enclosed graduated dosing syringe. Use with caution in cats with renal dysfunction or impaired liver function. If clinical signs suggestive of liver dysfunction develop, treatment should be discontinued. ITRAFUNGOL oral solution is a cytochrome P-450 inhibitor and may increase or prolong plasma concentrations of other drugs metabolized by this pathway. Cats suffering from heart disease should be carefully monitored during treatment. The most common adverse reactions reported in clinical trials were elevated hepatic enzymes and gastrointestinal upset such as increased salivation, vomiting, diarrhea, and decreased appetite.

See package insert at end of the Product Guide for full product information.

1. Chermette, R., Ferreiro, L. & Guillot, J. Mycopathologia 2008 166: 385

KETOCHLOR® (Chlorhexidine Gluconate, Ketoconazole) Medicated Shampoo

- An antiseptic shampoo for the management of conditions responsive to ketoconazole or chlorhexidine in dogs and cats
  - **Defensin technology** promotes natural skin microbial defenses with natural plant extracts
- Antimicrobial peptides (defensins) have been shown to reduce the exposure time and chlorhexidine concentration needed to achieve bactericidal efficacy[1]
- Specifically designed to meet the needs of dogs and cats with skin microbial imbalances, its antiseptic and cleansing properties help manage bacterial and fungal skin infections in dogs and cats
  - Neutralizes unpleasant odors
  - **Glycotechnology** provides microorganism anti-adhesive effects

Available in:

8 fl oz (237 mL) SKU 002908
16 fl oz (473 mL) SKU 002916

ALLERMYL® (Piroctone Olamine) Medicated Shampoo

- A hypoallergenic medicated shampoo to repair, protect and manage the skin of allergic/atopic patients
- Soothing and moisturizing
- No fragrance, pigments or other irritating ingredients
- With S-I-S SKIN INNOVATIVE SCIENCE® Technology, ALLERMYL Shampoo is a hypoallergenic shampoo for the management of allergic skin conditions. Specifically designed to meet the needs of dogs and cats with sensitive and itchy skin, ALLERMYL Shampoo is a unique micro-emulsified formulation that combines ingredients that help:
  - Maintain skin barrier integrity
  - Provide moisturizing and soothing effect (Skin Lipid Complex)
  - Promote a healthy microbial balance in animals with allergic skin conditions (Piroctone Olamine)
  - **Defensin technology** promotes natural skin microbial defenses by supporting the immune response — antimicrobial peptides (AMPs) with natural plant extracts
  - **Glycotechnology** provides microorganism anti-adhesive effects

Available in:
8 fl oz (237 mL) SKU 002409
16 fl oz (473 mL) SKU 002417

KERATOLUX® (Piroctone Olamine) Medicated Shampoo

- With S-I-S SKIN INNOVATIVE SCIENCE® Technology, KERATOLUX Shampoo is a unique tar-free cleanser that removes scales, crusts and excessive oil on the skin surface of dogs and cats for management of keratoseborrheic conditions. With regular bathing, KERATOLUX Shampoo helps manage normal sebum production, resulting in a pleasant smell and healthy appearance to the skin coat

KERATOLUX Shampoo:

- **Defensin technology** promotes natural skin microbial defenses with natural plant extracts by supporting the innate immune response — antimicrobial peptides (AMPs)
- Improves hair and skin balance
- Removes excess sebum and scales
- Neutralizes unpleasant odors
- **Glycotechnology** provides microorganism anti-adhesive effects
- Promotes a healthy microbial balance in animals with keratoseborrheic conditions (Piroctone Olamine)

Available in:
8 fl oz (237 mL) SKU 002009
16 fl oz (473 mL) SKU 002017

1. Santoro D, Kher L, Chala V, Navarro C. Evaluation of the effects of chlorhexidine digluconate with and without cBD103 or cCath against multidrug-resistant clinical isolates of Staphylococcus pseudintermedius. *Vet Dermatol.* 2022;33(1):17-e6. doi:10.1111/vde.13018.

ALLERDERM® Foaming Cleanser

- No water, no fuss, no stress foaming gentle cleanser
- For gentle and quick cleaning between baths, with no water required.
- Micellar water solution adapted to use on any skin type, even sensitive skin
- Easy-to-use foam application
- Neutral pH, nonirritating formula

Available in:
6.76 oz SKU 13500

ALLERDERM® OMEGADERM® Essential Fatty Acids Supplement

- A unique nutritional supplement containing omega-3 and omega-6 essential fatty acids
- Formulated for dogs and cats
- Once-daily supplement
- Ideal for maintaining healthy skin and hair coat
- Premeasured EZ-dose packets
- High palatability and product acceptance when poured over food

Available in: 28-count dispensers
4 mL for small dogs and cats < 20 lbs SKU 14149
8 mL for medium and large dogs > 20 lbs SKU 14186

EPI-SOOTHE® Cream Rinse

Formulated for dry and sensitive skin in dogs, cats and horses of any age. This unique formula helps restore natural skin oils and moisture, makes the hair coat more manageable and helps prevent tangles while adding a high sheen to the hair coat.

Available in:
8 fl oz (237 mL) SKU 001808
16 fl oz (473 mL) SKU 001816

EPI-SOOTHE® Shampoo

Natural oat-grain derivative, soap-free shampoo designed for soothing and cleansing dry and sensitive skin in dogs, cats and horses of any age.

Available in:
8 fl oz (237 mL) SKU 11708
16 fl oz (473 mL) SKU 11716

ALLERGROOM® Shampoo

Gentle, soap-free moisturizing shampoo designed for frequent use on normal to dry skin to optimize the skin and hair coat of dogs, cats and horses of any age.

Available in:
8 fl oz (237 mL) SKU 12208
16 fl oz (473 mL) SKU 12216

A recent study found that more than 60% of Golden Retrievers were not protected from heartworm disease.[1] Heartworm infection incidence continues trending upward in the general pet population.[2]

IVERHART MAX® Chew (ivermectin/ pyrantel pamoate/praziquantel)

- An affordable heartworm protection option for dogs 8 weeks of age or older
- Prevents heartworm disease
- Treats and controls roundworms, hookworms and tapeworms
- Satisfaction guaranteed
- Administer every 30 days, year-round
- Bacon-flavored

Available in four sizes, depending on the dog's weight:
Toy: 6-12 lbs SKU 50102
Small: 12.1-25 lbs SKU 50104
Medium: 25.1-50 lbs SKU 50106
Large: 50.1-100 lbs SKU 50108

For dogs over 100 lbs, use the appropriate combination of these chews.

6-dose card display box / 10 cards per display (60 doses)

Important Safety Information
IVERHART MAX® Chew (ivermectin/pyrantel pamoate/praziquantel) is well tolerated. All dogs should be tested for heartworm disease before starting a preventive protocol. Following the use of IVERHART MAX Chew, gastrointestinal and neurological side effects have been reported.

See package insert at the end of the Product Guide for full product information.

IVERHART PLUS® (ivermectin/pyrantel) *Flavored Chewables*

- An affordable heartworm protection option for dogs 6 weeks of age or older
- Prevents heartworm disease
- Treats and controls roundworm and hookworm infections in dogs
- Satisfaction guaranteed
- Administer every 30 days, year-round
- Pork liver-flavored

Available in three sizes, depending on the dog's weight:
Small: < 25 lbs SKU 0170DS
Medium: 26-50 lbs SKU 0170DM
Large: 51-100 lbs SKU 0170DL

For dogs over 100 lbs, use the appropriate combination of these chews.

6-dose card display box / 10 cards per display (60 doses)

Important Safety Information
IVERHART PLUS® (ivermectin/pyrantel) *Flavored Chewables* is well tolerated. All dogs should be tested for heartworm disease before starting a preventive protocol. There are rare reports of digestive or neurological side effects following use of *IVERHART* PLUS *Flavored Chewables*.

See package insert at the end of the Product Guide for full product information.

1. Wisnieski L, Faulkner V, Faulkner C. Factors associated with heartworm preventative use in the golden retriever lifetime study. *Front Vet Sci.* 2023;10:1208804. doi:10.3389/fvets.2023.1208804

2. New American Heartworm Society heartworm incidence map reveals upward trend in heartworm cases. *American Heartworm Society*. April 11, 2023. Accessed February 18, 2025. https://www.heartwormsociety.org/in-the-news/825-new-american-heartworm-society-heartworm-incidence-map-reveals-upward-trendinheartworm-cases

A recent study found that more than 60% of Golden Retrievers were not protected from heartworm disease.[1] Heartworm infection incidence continues trending upward in the general pet population.[2]

PARASEDGE® Multi for Dogs (imidacloprid + moxidectin) Topical Solution

- An affordable flea and heartworm protection option for dogs
- Prevents heartworm disease
- Treatment of *Dirofilaria immitis circulating microfilariae* in heartworm positive dogs
- Kills adult fleas and is indicated for the treatment of flea infestations
- Treatment and control of sarcoptic mange, hookworms, roundworms and whipworms
- Administer topically every 30 days, year-round
- The safe use has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs body weight
- Satisfaction guaranteed

Available in five sizes depending on dog's weight:
Toy: Dogs 3-9 lbs SKU 51115
Small: Dogs 9.1-20 lbs SKU 51116
Medium: Dogs 20.1-55 lbs SKU 51117
Large: Dogs 55.1-88 lbs SKU 51118
3-dose card display box / 10 cards per display (30 doses)
X-Large: Dogs 88.1-110 lbs SKU 51119
3-dose card display box/5 cards per display (15 doses)

Important Safety Information
PARASEDGE® Multi for Dogs (imidacloprid + moxidectin) Topical Solution: Children should not come in contact with the application site for two (2) hours after application. Wash hands after use. Do not use this product on cats. DO NOT ADMINISTER THIS PRODUCT ORALLY. Do not use on puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight. Ensure that dogs cannot lick the product on themselves or other treated pets for 30 minutes after application. Use with caution on sick, debilitated, or underweight dogs. Safety in breeding, pregnant, or lactating dogs has not been established.

See package insert at the end of the Product Guide for full product information.

PARASEDGE™ Multi for Cats (imidacloprid + moxidectin) Topical Solution

- An affordable flea and heartworm protection option for cats and ferrets
- Prevents heartworm disease in cats and ferrets
- Kills adult fleas and is indicated for the treatment of flea infestations on cats and ferrets
- Treatment and control of ear mite infestations, hookworms and roundworms in cats
- Administer topically every 30 days, year-round
- Do not use in cats less than 9 weeks of age or less than 2 lbs
- Satisfaction guaranteed

Available in three sizes depending on cat's weight:
Cats 2-5 lbs SKU 51120
Cats 5.1-9 lbs SKU 51121
Cats 9.1-18 lbs SKU 51122
Ferrets 2-4.4 lbs SKU 51121
3-dose card display box/10 cards per display (30 doses)

Important Safety Information
PARASEDGE™ Multi for Cats (imidacloprid + moxidectin) Topical Solution: Children should not come in contact with the application site for 30 minutes after application. Wash hands after use. DO NOT ADMINISTER THIS PRODUCT ORALLY. Do not use on sick, debilitated or underweight cats or ferrets. CATS: Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight. Evaluation in geriatric cats with subclinical conditions, and safety in breeding, pregnant or lactating cats has not been established. FERRETS: Use only the 0.4 mL PARASEDGE Multi for Cats in ferrets. Treatment of ferrets weighing less than 2.0 lbs (0.9 kg) should be based on a risk-benefit assessment. The effectiveness in ferrets weighing over 4.4 lbs (2.0 kg) or the safety in breeding, pregnant and lactating ferrets has not been established.

See package insert at the end of the Product Guide for full product information.

1. Wisnieski L, Faulkner V, Faulkner C. Factors associated with heartworm preventative use in the golden retriever lifetime study. *Front Vet Sci.* 2023;10:1208804. doi:10.3389/fvets.2023.1208804

2. New American Heartworm Society heartworm incidence map reveals upward trend in heartworm cases. American Heartworm Society. April 11, 2023. Accessed February 18, 2025. https://www.heartwormsociety.org/in-the-news/825-new-american-heartworm-society-heartworm-incidence-map-reveals-upward-trendinheartworm-cases

HEARTWORM & PARASITICIDES

SENERGY™ (selamectin) for Cats and Dogs

Indications:

- An affordable flea and heartworm protection option for dogs and cats
- Kills adult fleas
- Prevention and control of flea infestations
- Prevention of heartworm disease
- Treatment and control of ear mites
- Treatment and control of hookworms and roundworms (cats only)
- Treatment and control of sarcoptic mange and control of tick infestations (dogs only)
- Administer topically every 30 days, year-round
- Quick drying

Available in eight sizes, depending on the dog's or cat's weight: Kitten (at least 8 weeks old) and Puppy (at least 6 weeks old):
Cats and Dogs: Up to 5 lbs SKU 50090
Cats: 5.1-15 lbs SKU 50095
Cats: 15.1-22 lbs SKU 50097
Dogs, Toy: 5.1-10 lbs SKU 50005
Dogs, Small: 10.1-20 lbs SKU 50010
Dogs, Medium: 20.1-40 lbs SKU 50020
Dogs, Large: 40.1-85 lbs SKU 50040
Dogs, X-Large: 85.1-130 lbs SKU 50085
3-dose card display box / 10 cards per display (30 doses)

Important Safety Information
SENERGY™ (selamectin) may be irritating to the skin and eyes for people. Wash hands after use. Do not use in sick, debilitated or underweight animals. All dogs should be tested for heartworm disease before starting a preventive protocol. Use only on cats that are at least 8 weeks old and dogs that are at least 6 weeks old.

See package insert at the end of the Product Guide for full product information.

EFFIPRO® PLUS Topical Solution for Cats

- Affordable flea and tick protection for cats
- One convenient dose for cats and kittens weighing 1.5 lbs or more
- Kills fleas, ticks and chewing lice
- Dual action of fipronil and pyriproxyfen to break the flea life cycle
- 1 application lasts 4 weeks
- Waterproof
- For use on cats and kittens 8 weeks or older

Active ingredients:

- Fipronil
- Pyriproxyfen

EFFIPRO® PLUS Topical Solution for Cats: Read entire label before each use.

Available in three applicators per carton:
For cats weighing 1.5 lbs and over SKU 60463
3-dose card display box / 10 cards per display (30 doses)

EFFIPRO® PLUS Topical Solution for Dogs

- Affordable flea and tick protection for dogs
- Kills fleas, ticks and chewing lice
- Dual action of fipronil and pyriproxyfen to break the flea life cycle
- Aids in the control of sarcoptic mites
- 1 application lasts 4 weeks
- Waterproof
- For use in dogs and puppies 8 weeks and older
- DO NOT USE ON CATS

Active ingredients:

- Fipronil
- Pyriproxyfen

EFFIPRO® PLUS Topical Solution for Dogs:
DO NOT USE ON CATS.
Read entire label before each use.

Available in four sizes, depending on dog's weight:
Small: 5-22.9 lbs SKU 60473
Medium: 23-44.9 lbs SKU 60483
Large: 45-88.9 lbs SKU 60503
X-Large: 89-132 lbs SKU 60513
3-dose card display box / 10 cards per display (30 doses)

EFFITIX® PLUS Topical Solution for Dogs

- The American Heartworm Society's 2024 canine heartworm guidelines recommend using a topical repellent product, in addition to a heartworm preventive, for further protection against disease vectors[1]
- Dual action of fipronil and pyriproxyfen to break the flea life cycle
- Kills fleas, flea eggs, flea larvae, and prevents the development of flea pupae, controlling and preventing flea infestations
- Repels and kills all stages of Deer Tick, Brown Dog Tick, Lone Star Tick and American Dog Tick
- Repels and kills mosquitoes
- Repels and reduces blood feeding by biting flies
- Kills lice and prevents further infestations
- Aids in the control of Sarcoptes mites
- Affordable, easy to apply, quick drying, waterproof
- Starts working on contact
- Only use on dogs and puppies 8 weeks or older

Active ingredients:

- Fipronil
- Permethrin
- Pyriproxyfen

EFFITIX® PLUS Topical Solution for Dogs:
DO NOT USE ON CATS.
Read entire label before each use.

Available in five sizes, depending on dog's weight:
Toy: 5-10.9 lbs SKU 60520
Small: 11-22.9 lbs SKU 60522
Medium: 23-44.9 lbs SKU 60524
Large: 45-88.9 lbs SKU 60526
X-Large: 89-132 lbs SKU 60528
3-dose card display box / 10 cards per display (30 doses)

1. American Heartworm Society canine guidelines for the prevention, diagnosis, and management of heartworm (Dirofilaria immitis) infection in dogs. Accessed May 21, 2024. https://d3ft8sckhnqim2.cloudfront.net/images/AHS_Canine_Guidelinesweb04APR2024.pdf?1712247474.

Virbantel® (pyrantel pamoate/praziquantel) Flavored Chewables

- Treats and control roundworms, hookworms and tapeworms at an affordable price
- Flavored chewables for dogs and puppies 12 weeks and older
- Palatable chewable tablets can be offered directly to the dog or administered with food

Available in 50 flavored chewables bottles:
30 mg for dogs 6.0-25 lbs SKU 54030
114 mg for dogs 25.1-200 lbs SKU 51114

Important Safety Information
Virbantel® (pyrantel pamoate/praziquantel) Flavored Chewables: Do not use in sick animals. Safety in breeding dogs and pregnant dogs has not been evaluated.

See package insert at the end of the Product Guide for full product information.

KNOCKOUT® Area Treatment

- Kills adult fleas, adult ticks and controls pre-adult fleas (larvae) for 120 days
- Treat pet bedding, carpet and upholstered furniture
- Apply this product only as specified on the labeling
- DO NOT TREAT PETS WITH THIS PRODUCT

Available in:
14 oz (397 g) aerosol can
SKU 612014

KNOCKOUT® E.S. Area Treatment

- Contains Nylar® insect growth regulator
- Kills active flea infestations
- Prevents flea reinfestations for 7 months
- Kills ticks
- One 16-ounce spray can treats up to 2,100 square feet
- Apply this product only as specified on the labeling
- DO NOT TREAT PETS WITH THIS PRODUCT

Available in:
16 oz (454 g) inverted aerosol can
SKU 612216

KNOCKOUT® Room and Area Fogger

- Kills adult fleas, preadult fleas and flea eggs for 7 months
- Reaches fleas and ticks (and other insects) in rugs, draperies, upholstery, pet bedding, floor cracks and open cabinets
- One 6-ounce fogger treats a room measuring up to 27 feet by 27 feet with an 8-foot ceiling
- For indoor use only
- Apply this product only as specified on the labeling
- Prevents flea reinfestations for 7 months
- DO NOT TREAT PETS WITH THIS PRODUCT

Available in:
6 oz (170 g) size SKU 612106

See full product labeling for Directions of Use and Cautionary statements.
Nylar is a registered trademark of McLaughlin McGormley King Company.

IN-CLINIC USE

EUTHASOL® (pentobarbital sodium and phenytoin sodium) Euthanasia Solution

- Intravenous solution for humane, painless and rapid euthanasia
- For dogs only

Available in:
100 mL multiple dose vials SKU 710101

Important Safety Information
EUTHASOL® (pentobarbital sodium and phenytoin sodium) Euthanasia Solution: WARNING: Keep out of reach of children. If eye contact, flush with water and seek medical advice/attention. CAUTION: Caution should be exercised to avoid contact of the drug with open wounds or accidental self-inflicted injections. For canine euthanasia only. Must not be used for therapeutic purposes. Do not use in animals intended for food. Euthanasia may be delayed in dogs with severe cardiac or circulatory deficiencies.

ENVIRONMENTAL HAZARD: This product is toxic to wildlife. Birds and mammals feeding on treated animals may be killed. Euthanized animals must be properly disposed of by deep burial, incineration, or other method in compliance with state and local laws, to prevent consumption of carcass material by scavenging wildlife. For full prescribing information, contact Virbac at 1-800-338-3659 or visit us.virbac.com.

See full prescribing information at the end of the Product Guide for complete boxed warning.

STELFONTA® (tigilanol tiglate injection)

The mast cell tumor treatment option pet owners prefer.[1] Treat mast cell tumors (MCTs) with a single intratumoral injection, without surgery or general anesthesia. STELFONTA is indicated for use in dogs for the treatment of non-metastatic mast cell tumors all over the body, and non-metastatic subcutaneous mast cells located at or distal to the elbow or the hock.

- 87% complete removal of mast cell tumor with one or two injections[2]
- 75% complete removal of mast cell tumor with one injection[2]
- Tumor sites typically healed within 28 days with minimal intervention[2]

Available in:
2 mL vial SKU 10101

Important Safety Information
Accidental self-injection of STELFONTA® (tigilanol tiglate injection) may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary. In dogs, do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock. Formation of wounds, possibly extensive, is an intended and likely response to treatment with STELFONTA along with associated swelling, bruising, and pain; these wounds are expected to heal. Appropriate pre- and post-treatment medications must be given, including a corticosteroid plus blocking agents for both H1 and H2 receptors, in order to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation.

See full prescribing information at the end of the Product Guide for complete boxed warning.

For more product information, scan the QR code.

1. Data on file. Virbac Corporation.
2. DeRidder TR, Campbell JE, Burke-Schwarz C, et al. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). *J Vet Intern Med*. 2021;35(1):415-429. doi: 10.1111/jvim.15806 doi:10.1111/jvim.15806

STELFONTA is a registered trademark of QBiotics Pty Ltd, used under license.

SUPRELORIN® F (deslorelin acetate) Implant

- For the management of adrenal gland cortical disease (ACD) in male and female domestic ferrets
- SUPRELORIN F suppresses the reproductive endocrine system, preventing production of pituitary and gonadal hormones
- Reduces clinical signs of ACD with a return to normalcy in 2-8 weeks[1-2]
- 4.7 mg dose implant has been shown to be well tolerated with clinical monitoring[1]

Available in:
2-count SKU 44402
5-count SKU 44405

Important Safety Information
SUPRELORIN® F (deslorelin acetate) Implant: For use in ferrets only. DO NOT HANDLE THIS PRODUCT IF YOU ARE PREGNANT OR NURSING OR SUSPECT YOU MAY BE PREGNANT. Accidental administration in humans may lead to disruption of the menstrual cycle. Do not use in animals intended for breeding. The safe use of this product has not been evaluated in pregnant or lactating ferrets. Do not use this product in ferrets with known hypersensitivity to deslorelin acetate or other synthetic hormones.

See package insert at the end of the Product Guide for full product information.

1. Wagner RA, Piché CA, Jöchle W, Oliver JW. Clinical and endocrine responses to treatment with deslorelin acetate implants in ferrets with adrenocortical disease. *Am J Vet Res*. 2005;66(5):910-914. doi:10.2460/ajvr.2005.66.910
2. Wagner RA, Finkler MR, Fecteau KA, Trigg TE. The treatment of adrenal cortical disease in ferrets with 4.7 mg deslorelin acetate implants. *J Exotic Pet Med*. 2009;18(2):146-152. doi:10.1053/j.jepm.2008.11.003

ZOLETIL® (tiletamine and zolazepam for injection)

- Nonnarcotic, nonbarbiturate, injectable anesthetic agent for dogs and cats
- Intramuscular and intravenous injection in dogs
- Intramuscular injection only in cats

Available in:
5 mL SKU 71805

Important Safety Information
ZOLETIL® for Injection should not be used 1) in dogs and cats with severe cardiac or pulmonary dysfunction, or pancreatic disease 2) at any stage of pregnancy or for Cesarean section, 3) in cats suffering from renal insufficiency 4) with phenothiazine-derivative drugs as the combination produces respiratory and myocardial depression, hypotension and hypothermia. Pulmonary edema has been reported in cats. Respiratory depression may occur following administration of high doses. Copious salivation that may occur during anesthesia can be controlled by concurrent administration of atropine sulfate. Reduce dosage in geriatric dogs and cats. Patients should be continuously monitored.

See package insert at the end of the Product Guide for full product information.

For more information, call 1-800-338-3659 or visit vet-us.virbac.com.

URSOLYX™ Soft Chews for Dogs

- First-in-its-class muscle support featuring ursolic acid, which targets mRNA expression in skeletal muscle. Promotes muscle function and strength in aging, active or recuperating patients
- NASC Quality Seal
- For use in dogs
- Bacon-flavored soft chew
- Made in the USA, including U.S. and globally sourced ingredients

Available in 60-count bottles:
Small: Up to 30 lbs (120 g / 4.2 oz) SKU 10620
Medium: 30-60 lbs (240 g / 8.5 oz) SKU 10621
Large: Over 60 lbs (360 g / 12.7 oz) SKU 10622

MOVOFLEX® Advanced Soft Chews

- Supplement designed to support dogs' short- and long-term mobility, flexibility and joint function for optimal joint health
- A complex balance of seven ingredients with synergistic function:
  - Eggshell Membrane, Astaxanthin, Boswellic Acid, Vitamin D_3, High Molecular Weight Hyaluronic Acid, Krill, Low Molecular Weight Hyaluronic Acid
- No loading period required for these tasty chicken-flavored chews
- For use in dogs
- NASC quality seal
- Eco-friendly packaging
- Made in the USA, including U.S. and globally sourced ingredients

Available in 60-count bottles:
Small: Up to 40 lbs (120 g / 4.2 oz) SKU 10418
Medium: 40-80 lbs (240 g / 8.5 oz) SKU 10419
Large: Over 80 lbs (360 g / 12.7 oz) SKU 10420

MOVODYL® Chewable Tablets (carprofen)

Indications:
- Nonsteroidal anti-inflammatory drug (NSAID) for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs
- Easy-to-administer scored tablet
- For use in dogs only

Available in flavored, chewable tablets:
25 mg (60 tablets) SKU 10021
75 mg (60 tablets) SKU 10022
100 mg (60 tablets) SKU 10023
25 mg (180 tablets) SKU 10024
75 mg (180 tablets) SKU 10025
100 mg (180 tablets) SKU 10026

Important Safety Information
MOVODYL® Chewable Tablets (carprofen): Not for human use. FOR USE IN DOGS ONLY. DO NOT USE IN CATS. As a class, NSAIDS may be associated with gastrointestinal, kidney and liver side effects. These are usually mild, but may be serious. Pet owners should discontinue therapy and contact their veterinarian immediately if side effects occur. Evaluation for pre-existing conditions and regular monitoring are recommended for pets on any medication, including MOVODYL Chewable Tablets. Use with other NSAIDS or corticosteroids should be avoided.

See package insert at the end of the Product Guide for full product information.

VETERINARY HPM® Spay & Neuter Diets

VHPM formulas are designed for proactive weight management, combining high protein, high fiber and reduced carbohydrates. Ideal for the **spayed and neutered pet.**

Supports:
- **Weight and Appetite Control:** Protein and fiber support optimal weight and help the pet feel full
- **Lean Muscle & Healthy Metabolism:** 84% animal-sourced protein aids in the development of lean muscle. While the right blend of high proteins, reduced carbohydrates and high fibers, helps supports a healthy metabolism and nourishes healthy growth
- **Healthy Digestion:** Prebiotics and dietary fiber support healthy digestion
- **Skin & Coat:** High level of proteins and balance of omega omega-6 / omega-3 fatty acids to nourish healthy skin and shiny coat
- **Tailored Nutrition for Juniors:** Provides balanced caloric intake for growing spayed/neutered puppies and kittens, meeting growth guidelines while promoting lean muscle and satiety

Available in:

Canine Diets:

Small & Toy Junior
3.0 lb bag SKU 10900
6.5 lb bag SKU 10901

Small & Toy Adult
3.0 lb bag SKU 10902
6.5 lb bag SKU 10903
15.0 lb bag SKU 10904

Large & Medium Junior
3.0 lb bag SKU 10905
15.0 lb bag SKU 10914
26.0 lb bag SKU 10906

Large & Medium Adult
3.0 lb bag SKU 10907
15.0 lb bag SKU 10915
26.0 lb bag SKU 10908

Feline Diets:

Junior
3.0 lb bag SKU 10909
6.5 lb bag SKU 10910

Adult
3.0 lb bag SKU 10911
6.5 lb bag SKU 10912
15.0 lb bag SKU 10913

Scan QR code to register your clinic and order, or visitivet.com/vets/signup/

Call 1-800-436-5909, fax 1-877-398-4838 or orders@ivet.com.

Formulated to meet the nutritional needs for growth or maintenance as established by AAFCO.

NutriCare™ Canine Diets

Supports:

- Specialized nutrition tailored to manage specific needs, such as weight reduction, heart and kidney support, digestive health and gastrointestinal support
- Incorporates highly digestible ingredients and prebiotics to promote both gastrointestinal health and nutrient absorption
- Developed in partnership with veterinarians, NutriCare™ Canine Diets ensures Advanced Care nutrition designed to address and support specific health indications

Available in:
Canine Digestive Support
6.6 lb SKU 017107
17.6 lb SKU 017117
33 lb SKU 017133

Canine Gastrointestinal Support-WET
13 oz / (369g) cans, 12 per case SKU 18299

Canine Weight Reduction
5 lb SKU 017205
15.4 lb SKU 017215
30 lb SKU 017230

Canine Heart & Kidney Support
8 lb SKU 017008
17.6 lb SKU 017018

Healthy Gourmet™ Pet Foods

- Features high quality protein, avoids soy and wheat, and includes digestibility-friendly elements like rice, oatmeal and barley
- Targeted Nutrition to address specific life stages and lifestyle needs, including enhanced nutrients for growth in puppies and kittens, and joint support for senior pets
- Enriched with antioxidants (Vitamins E, C, Beta-Carotene) for immune support, omega-3 and omega-6 fatty acids for skin and coat health
- Recipes cater to growth, aging seniors, weight management and the special needs of felines
- Preserved with mixed tocopherols, a source of Vitamin E

Available in:
Canine Diets:

Canine Adult
6.6 lb SKU 015207
17.6 lb SKU 015217
33 lb SKU 015233
12 - 13 oz /(369g) cans SKU 018099

Canine Senior
6.6 lb SKU 015407
17.6 lb SKU 015417
33 lb SKU 015433

Canine Reduced Fat
6.6 lb SKU 015307
17.6 lb SKU 015317
33 lb SKU 015333

Large Breed Puppy
6.6 lb SKU 015107
17.6 lb SKU 015117
33 lb SKU 015133

Small Breed Puppy
6.6 lb SKU 015007
17.6 lb SKU 015017

Feline Diets:

Feline Adult
3.3 lb SKU 020202
17.6 lb SKU 020217
24 - 5.5 oz (155.9g) cans SKU 028199

Feline Senior
3.3 lb SKU 020402
17.6 lb SKU 020417

Feline Reduced Fat
3.3 lb SKU 020302
17.6 lb SKU 020317

Kitten
3.3 lb SKU 020102
17.6 lb SKU 020117

Formulated to meet the nutritional needs for growth or maintenance as established by AAFCO.

PET NUTRITION

PET NUTRITION

COLDWATER CULINARY™ Canine Diet

- Simplified ingredients for dogs with food and skin sensitivities. Our limited ingredient recipe is crafted with salmon as the single source of fish protein, making it suitable for dogs with sensitive dietary needs
- Includes a blend of natural antioxidants derived from various fruits and vegetables to help support a healthy immune system
- Added prebiotics help aid in digestion and promote a healthy gut environment
- Enriched with omega-3 and omega-6 fatty acids, which play a crucial role in maintaining a healthy skin and coat. These essential fatty acids can help support the skin's natural barrier function, and promote a shiny, well-nourished coat

Available in:
Canine Adult Salmon & Potato
5 lb SKU 012005
17.6 lb SKU 012017

VetBasics™ Dog Foods

- VetBasics™ provides an affordable option, offering optimal nutrition to suit the dog's lifestyle
- VetBasics™ includes Maintenance for general wellness and Energy for active dogs with higher caloric needs

Available in:
Canine Energy
33 lb SKU 010233

Canine Maintenance
33 lb SKU 010133

Formulated to meet the nutritional needs for growth or maintenance as established by AAFCO.

Healthy Rewards™ Canine Low Fat Treats

- Low in fat and calories: Each treat contains less than 6 calories, helping maintain your pet's healthy weight
- Made with fresh chicken, no soy, and no wheat, ensuring excellent taste and palatability
- Smaller size is perfect for training or fun. Great for reinforcing positive behavior, training, or simply rewarding your dog

Available in:
8 oz. SKU 031103
12 - 8 oz (case) SKU 031102

SensiSnacks™ Hydrolyzed Low Fat Canine Treat

- For food and skin sensitivities: Designed as a more appropriate treat for dogs with allergies or skin sensitivities
- Features a single protein source (hydrolyzed chicken liver) and a single carbohydrate source (dried potato)
- Semi-moist, soft, easy-to-chew treats suitable for dogs of all ages
- Highly palatable

Available in:
8 oz SKU 031205
12 - 8 oz per case SKU 31201

How to Order. Getting started is easy!

iVet.com

Register Your Clinic:
Visit **ivet.com/vets/signup** to create your clinic's account.

Flexible Ordering Options:

- **Clinic Orders:** Purchase directly from iVet.com and stock products for sale in your clinic.
- **Client Home Delivery:** For inventory-less product ordering, refer clients to iVet.com for easy ordering and fast delivery. Best of all, your clinic will be credited for each order!

Fast Delivery | Special Promotions | 100% Guarantee | Vet-Pet Bond

SUPPLEMENTS

NEPHRODYL™ Synbiotic Capsules

- Proprietary detoxifying blend of prebiotics and probiotics that supports optimal kidney function
- Efficient storage with no need for refrigeration until opened
- Easy administration
- For use in dogs and cats

Available in:
60 capsules SKU 12620

REBOUND® Recuperation Formula for Dogs

- Helps support pet's nutrition needs during recuperation
- Balanced, fortified nutrition in a low-calorie liquid formula
- Palatable and easy to administer
- No added preservatives or colorants
- Intended for intermittent or supplemental feeding
- For use in dogs

Available in:
Formula for Dogs:
5.1 fl oz (150 mL)
SKU 10850

REBOUND® Recuperation Formula for Cats

- Helps support pet's nutrition needs during recuperation
- Balanced, fortified nutrition in a low-calorie liquid formula
- Palatable and easy to administer
- No added preservatives or colorants
- Intended for intermittent or supplemental feeding
- For use in cats

Available in:
Formula for Cats:
5.1 fl oz (150 mL)
SKU 10851

LIVESTOCK

BOVIGEN™ Platinum 5 Vaccine

- Manage risk with Platinum Protection
- BOVIGEN™ Platinum 5 Vaccine provides comprehensive protection against the most prevalent strains of bovine viral diarrhea virus (BVD) in the country, including BVD types 1 and 2. Vaccine strain BVD 1a has demonstrated effectiveness against 1b[2] and effectively protects against infectious bovine rhinotracheitis virus (IBR), bovine parainfluenza 3 virus (PI3) and bovine respiratory syncytial virus (BRSV)
- Safe for use in weaned calves as part of preconditioning and value-add programs and replacement heifer development programs
- Provides protection against BVD type 1a, 1b[2] and BVD type 2
- Labeled for use in pregnant cows and calves nursing pregnant cows provided they were vaccinated 30 to 60 days pre-breeding with BOVIGEN Platinum 3, BOVIGEN Platinum 3 LP, BOVIGEN Platinum 5 or BOVIGEN Platinum 5 L5 Vaccines. Do not vaccinate within 21 days of slaughter

Available in:

10 ds SKU 66721
50 ds SKU 66722

Important Safety Information
Scan below for additional information. See package Insert at the end of this Product Guide for indications and instructions for use.

BOVIGEN™ Platinum 5 L5 Vaccine

- Protect your future calves with Platinum protection
- BOVIGEN™ Platinum 5 L5 Vaccine protects cows and replacement heifers from abortion-causing bacteria like *leptospirosis*, and viruses that lead to reproductive issues, including bovine viral diarrhea virus (BVD) types 1 and 2, infectious bovine rhinotracheitis virus (IBR), bovine parainfluenza 3 virus (PI3) and bovine respiratory syncytial virus (BRSV)
- It offers cross-protection against *Leptospira hardjo-bovis* and comprehensive protection against *Leptospira canicola, Leptospira grippotyphosa, Leptospira hardjo, Leptospira icterohaemorrhagiae, Leptospira pomona* and the most prevalent strains of BVD in the country[3,4]
- Provides protection against BVD type 1a, 1b[2] and BVD type 2
- Labeled for use in pregnant cows and calves nursing pregnant cows provided they were vaccinated 30 to 60 days pre-breeding with BOVIGEN Platinum 3, BOVIGEN Platinum 3 LP, BOVIGEN Platinum 5 or BOVIGEN Platinum 5 L5 Vaccines. Do not vaccinate within 21 days of slaughter

Available in:
10 ds SKU 66723
50 ds SKU 66724

Important Safety Information
Scan below for additional information. See package Insert at the end of this Product Guide for indications and instructions for use.

BOVIGEN™ Platinum 3 Vaccine

- Protect your investment and ensure cattle are ready for market with essential Platinum Protection
- BOVIGEN™ Platinum 3 Vaccine has been shown to be effective for the vaccination of healthy cattle against infectious bovine rhinotracheitis virus (IBR), bovine virus diarrhea virus Type I (BVD), bovine virus diarrhea virus Type II (BVD). BOVIGEN Platinum 3 Vaccine has also demonstrated effective cross protection against BVD 1b[2] Therefore, BOVIGEN Platinum 3 Vaccine is ideal for use in feedlot cattle and those cattle that need targeted respiratory protection
- Provides protection against BVD type 1a, 1b[2] and BVD type 2
- Labeled for use in pregnant cows and calves nursing pregnant cows provided they were vaccinated, 30 to 60 days pre-breeding, with BOVIGEN™ Platinum 3, BOVIGEN™ Platinum 3 LP, BOVIGEN™ Platinum 5, or BOVIGEN™ Platinum 5 L5 Vaccines. Do not vaccinate within 21 days of slaughter

Available in:
50 ds SKU 66731

Important Safety Information
Scan below for additional information. See package Insert at the end of this Product Guide for indications and instructions for use.

BOVIGEN™ Platinum 3 LP Vaccine

- For added protection against *Leptospira pomona*, choose Platinum protection that's ideal for feedyards or calf ranches
- BOVIGEN™ Platinum 3 LP Vaccine has been shown to be effective for the vaccination of healthy cattle against infectious bovine rhinotracheitis virus (IBR), bovine virus diarrhea virus Type I (BVD), bovine virus diarrhea virus Type II (BVD), and *Leptospira pomona*. This added Leptospira component makes BOVIGEN Platinum 3 LP Vaccine ideal for use in feedyards and calf ranches. BOVIGEN Platinum 3 LP Vaccine has also demonstrated effective cross protection against BVD 1b[2]
- Provides protection against BVD type 1a, 1band BVD type 2
- Labeled for use in pregnant cows and calves nursing pregnant cows provided they were vaccinated, 30 to 60 days pre-breeding, with BOVIGEN™ Platinum 3, BOVIGEN™ Platinum 3 LP, BOVIGEN™ Platinum 5, or BOVIGEN™ Platinum 5 L5 Vaccines. Do not vaccinate within 21 days of slaughter

Available in:
50 ds SKU 66733

Important Safety Information
Scan below for additional information. See package Insert at the end of this Product Guide for indications and instructions for use.

Scan here for additional information. See package Insert at the end of this Product Guide for indications and instructions for use

1. Fulton RW, Cook BJ, Payton ME, et al. Immune response to bovine viral diarrhea virus (BVDV) vaccines detecting antibodies due to BVDV subtypes 1a, 1b, 2a and 2c. *Vaccine* 2020;38(24):4032–4037. **2.** Data on file. Diamond Animal Health. **3.** Fulton, RW, Ridpath, JF, Saliki, JT, Briggs, RE, Confer, AW, Burge, LJ, Purdy, CW, Loan, RW, Duff, GC, Payton, ME, Bovine viral diarrhea virus (BVDV) 1b: predominant BVDV subtype in calves with respiratory disease. *The Canadian Journal of Veterinary Research* 2002;66:181-190. **4.** Xue, W, Mattick, D, Smith, L, Umbaugh, J, Trigo, E. Vaccination with a modified-live bovine viral diarrhea virus (BVDV) type 1a vaccine completely protected calves against challenge with BVDV type 1b strains. *Vaccine* 2010;29(1):70-76.

Tulissin® 25 (tulathromycin injection) Injectable Solution

Swine:

Tulathromycin, a first choice therapy[1] for treating swine respiratory disease (SRD):

- Goes to work in minutes[2]
- Concentrates in the most susceptible areas of the respiratory system
- Provides nine days of lung activity to treat and control SRD[3]

Cattle:

- Tulissin 25 Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis*

Available in:
100 mL bottle (20 bottles/case) SKU 66701
250 mL bottle (15 bottles/case) SKU 66702

Important Safety Information
TULISSIN® 25 (tulathromycin injection): Not for use in ruminating cattle. Ensure a preslaughter withdrawal time of twenty-two (22) days in calves and five (5) days in swine. The effects of tulathromycin on bovine and swine reproductive performance, pregnancy and lactation have not been determined. Do not use in animals known to be hypersensitive to the product.

See package insert at the end of the Product Guide for full prescribing information.

Tulissin® 100 (tulathromycin injection) Injectable Solution

Based on the trusted active ingredient tulathromycin, TULISSIN 100 Injectable Solution offers:

- Fast-acting treatment and control of bovine respiratory disease (BRD) and swine respiratory disease (SRD)
- Single shot convenience with 18-day preslaughter withdrawal period in cattle and five days in swine
- Also indicated for the treatment of infectious bovine keratoconjunctivitis (also known as pinkeye) and foot root in cattle
- Patented[4] protective shell on the 250 mL and 500 mL vials against breakage, providing 92% resistance[4] when dropped multiple times from a height of up to four feet[5]

Available in:
50 mL bottle (48 bottles/case) SKU 66703
100 mL bottle (20 bottles/case) SKU 66704
250 mL bottle (12 bottles/case) SKU 66705
500 mL bottle (6 bottles/case) SKU 66706

Important Safety Information
TULISSIN® 100 (tulathromycin injection): Not for use in humans. Ensure a pre-slaughter withdrawal time of eighteen (18) days in cattle and five (5) days in swine. Do not use in dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. The effects of tulathromycin on bovine and swine reproductive performance, pregnancy and lactation have not been determined. Do not use in animals known to be hypersensitive to the product.

See package insert at the end of the Product Guide for full prescribing information.

1. CEESA data, Q2 2021, injectable antibiotics brands used in swine segment. **2.** Villarino N, Brown SA, Martin-Jimenez T. Understanding the pharmacokinetics of tulathromycin: a pulmonary perspective. *J Vet Pharmacol Ther.* 2014;37(3):211-221. doi:10.1111/jvp.12080 **3.** Waag TA, Bradford JR, Lucas MJ, et al. Duration of effectiveness of tulathromycin injectable solution in an Actinobacillus pleuropneumoniae respiratory-disease challenge model in swine. *J Swine Health Prod.* 2008;16(3):126–130.

LIVESTOCK

Tenotryl™ (enrofloxacin) Injectable Solution

Cattle:

- For treatment and control of bovine respiratory disease (BRD)
- Designed to be fast and reliable[4]. One shot, two active molecules. Once injected into cattle, enrofloxacin is metabolized into enrofloxacin and ciprofloxacin[6]
- Convenience of single or multiple doses
- Adaptable injection supports judicious use of antibiotics

Swine:

- For treatment and control of swine respiratory disease (SRD) and control of colibacillosis
- Convenient, single-dose use

Available in:
100 mL bottle (20 bottles/case) SKU 66716
250 mL bottle (15 bottles/case) SKU 66717
500 mL bottle (6 bottles/case) SKU 66718

Cattle Important Safety Information
Tenotryl™ (enrofloxacin) 100 mg/mL Antimicrobial Injectable Solution: Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. This product is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in the calves born to these cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not exceed a 20 mL dose per injection site. Federal (USA) law prohibits the extra-label use of this drug in food producing animals.

Swine Important Safety Information
Tenotryl™ (enrofloxacin) 100 mg/ml Antimicrobial Injectable Solution: Animals intended for human consumption must not be slaughtered within 5 days of receiving a single injection dose. To assure responsible antimicrobial drug use, enrofloxacin should only be used as a second-line drug for colibacillosis in swine following consideration of other therapeutic options. Federal (USA) law prohibits the extra-label use of this drug in food producing animals.

See package insert at the end of the Product Guide for full prescribing information.

4. Patent application n°WO2019201812 Registered international design n°DM/103483. **5.** Internal study. **6.** McKellar Q, Gibson I, Monteiro A, Bregante M. Pharmacokinetics of enrofloxacin and danofloxacin in plasma, inflammatory exudate, and bronchial secretions of calves following subcutaneous administration. *Antimicrob Agents Chemother.* 1999;43(8):1988-1992. doi:10.1128/AAC.43.8.1988

PRODUCT INSERTS/DISCLOSURES

AYRADIA™
(metronidazole oral suspension) for dogs
125 mg/mL

For Oral Use in Dogs Only
Antimicrobial

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

Description
AYRADIA™ (metronidazole oral suspension) for dogs contains metronidazole USP. Metronidazole is a nitroimidazole, in the drug class anti-infectives, with anti-bacterial and anti-protozoal activities. The product is a flavored oily suspension with brown visible particles. The chemical composition of metronidazole is 2-(2-methyl-5-nitroimidazol-1-yl) ethanol. The empirical formula of metronidazole is: $C_6H_9N_3O_3$.
AYRADIA oral suspension contains 125 mg metronidazole/mL in a flavored, medium-chain triglyceride, liquid base.

Indication
AYRADIA oral suspension is indicated for the treatment of *Giardia duodenalis* infection in dogs.

Dosage and Administration
Shake vigorously before use.
AYRADIA oral suspension is administered orally at a dose of 25 mg/kg (11.3 mg/lb) of body weight, using the supplied syringe, twice daily for five consecutive days. Each line on the included dosing syringe represents 0.1 mL of oral suspension. For dogs weighing more than 15 kg (33 lb), the total dose volume will be divided over multiple syringe draws because the dosing syringe only holds up to 3 mL. Alternatively, a standard luer lock syringe that holds more than 3 mL can also be used. The flavored suspension can be administered directly into the mouth or in a small amount of food (see **Instructions for Using the Dispensing System and Preparing a Dose of AYRADIA oral suspension** on reverse side).

Contraindications
The use of this drug is contraindicated in animals with a history of a hypersensitivity to nitroimidazole compounds, including metronidazole.

Warnings

User Safety Warnings
Keep out of reach of children. Not for use in humans. Metronidazole has been found to cause cancer in laboratory animals; however, there is inadequate evidence of carcinogenicity in humans. People with known sensitivity to metronidazole or other nitroimidazole derivatives should avoid contact with AYRADIA oral suspension. This product is not a dermal or eye irritant but is a skin sensitizer which can potentially cause allergic contact dermatitis. Wash hands after use. Avoid contact with skin. In case of skin contact, wash the affected area thoroughly. Persons who come in contact with the dog's saliva during the first five minutes after administration should wash their hands. If the drug has been applied to dog food, the dog food should be kept away from children until after the dog has finished eating. Avoid accidental ingestion. In case of accidental ingestion, seek medical advice immediately.

Animal Safety Warnings
Federal law prohibits the extra-label use of this drug in food-producing animals.

Keep AYRADIA oral suspension in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions
Prescribing antimicrobial drugs in the absence of a proven or strongly suspected infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug resistant animal pathogens.

Use with caution in dogs with hepatic dysfunction.

Adverse neurologic effects have been associated with AYRADIA oral suspension use at high doses (see **Target Animal Safety**), but individual variation in sensitivity of dogs to the adverse neurologic effects of metronidazole has been reported.

The safe use of this drug in dogs intended for breeding purposes and in pregnant or lactating bitches has not been evaluated.

Adverse Reactions
In a clinical field effectiveness and safety study, 120 dogs were treated with AYRADIA oral suspension and 60 dogs were treated with a vehicle control. The most frequently reported adverse reactions were diarrhea (6.7% treated, 5% vehicle) and vomiting (4.2% treated, 3.3% vehicle). One dog treated with AYRADIA oral suspension was reported to have hyperactivity while being treated.

The safety of AYRADIA oral suspension was also evaluated in a masked, active-controlled, multi-site field study, to evaluate the effectiveness of AYRADIA oral suspension for the treatment of *Giardia* spp. in dogs. Enrollment included 180 client-owned dogs diagnosed with *Giardia* spp. infection; 91 dogs were treated with AYRADIA oral suspension at 25 mg/kg twice daily for 5 consecutive days and 89 were treated with an active control. The dogs were 7.8 weeks to 13.4 years old, various pure or mixed breeds, and intact or neutered male dogs or intact or spayed female dogs. The most frequently reported adverse reactions in dogs treated with AYRADIA oral suspension were vomiting (14.3%) and diarrhea (3.3%). Other less frequently reported (<1.2%) adverse reactions included hypersalivation, abdominal pain, polydipsia and polyuria, anorexia, otitis externa, and lethargy.

Contact Information
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. 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
Mechanism of Action
Metronidazole is a nitroimidazole compound known to exert antiprotozoal and antibacterial activity. Metronidazole has antiprotozoal activity against *Giardia duodenalis*. The mechanism of action for its antiprotozoal activity is not well understood but it acts primarily against the trophozoite forms of the parasites resulting in a decrease in cyst shedding. Metronidazole is reduced as it enters the susceptible target cell where it interacts with bacterial or protozoal DNA, causing a loss of helical structure and strand breakage in the DNA. This breakage leads to the inhibition of nucleic acid synthesis and therefore causes death of the bacterial or protozoal cell.

Pharmacokinetics
Metronidazole is a moderately lipophilic, low molecular weight, weak base that penetrates cell membranes and is well absorbed systemically.

The pharmacokinetics of AYRADIA oral suspension were evaluated in a cross-over study in 6 male and 6 female Beagle dogs receiving a single oral dose of 25 mg/kg metronidazole in the fed or fasted state. Following overnight fasting, half the dogs were fed a meal of dry dog food 15 minutes before dosing and the other dogs continued to be fasted until 4 hours post metronidazole administration. Blood samples were collected prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 30, and 48 hours post- dosing. Plasma concentrations of metronidazole were measured using a liquid chromatography with mass spectrometry detection method.

Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters for Plasma Metronidazole.

Parameter	Fasted	Fed
T_{max}[a] (hour)	1.50 (0.50-4.0)	1.50 (0.5-12)
C_{max} (µg/mL)	25.6 ± 7.2	15.6 ± 4.8
AUC_{last} (µg*h/mL)	153.7 ± 35.8	124.6 ± 37.3
$t_{1/2}$ (hour)	3.5 ± 1.3	3.7 ± 1.3

[a] Median and Range
T_{max} = time to maximum plasma concentration
C_{max} = maximum plasma concentration
AUC_{last} = area under the curve from the time of dosing to the last quantifiable plasma concentration
$t_{1/2}$ = elimination half-life

The maximum plasma concentration (C_{max}) and area under the curve from the time of dosing to the last quantifiable plasma concentration (AUC_{last}) for metronidazole were 39 and 20% lower, respectively, in the fed state, as compared to the fasted state. In a separate cross-over study, following oral and intravenous administration of 25 mg/kg metronidazole to twelve Beagle dogs, the mean absolute bioavailability, clearance (CL), and volume of distribution (Vd) of metronidazole oral suspension were 97.6%, 118 mL/hour/kg, and 628 mL/kg, respectively.

Effectiveness
The effectiveness of AYRADIA oral suspension was demonstrated in one dose confirmation laboratory study and one field effectiveness and safety study. AYRADIA oral suspension was administered at a dose of
25 mg/kg twice daily for five consecutive days in both studies.

The dose confirmation laboratory study was a parallel, masked, negative (sterile water) controlled study to evaluate effectiveness in naturally occurring *Giardia duodenalis* infection in dogs based on post-treatment intestinal trophozoite counts. The study included 13 healthy beagle dogs naturally infected with *Giardia* with pre-treatment cyst counts of ≥ 750 cysts/gram feces. The dogs were between 8.1 and 10.9 months of age and weighed between 9.8 and 14.6 kg (21.6 and 32.2 lbs). A statistically significant difference in trophozoite counts on Day 8, four days after the last dose, was detected in the AYRADIA-treated group as compared to the control group (geometric mean counts in the control group = 339,617 versus 1,056 in the treated group; p = 0.0026). The relative difference between the AYRADIA-treated group and the control group was calculated to be 99.7%.

The field effectiveness and safety study was a double-masked, vehicle-controlled, randomized, multi-center study conducted at veterinary clinics and shelters or non-breed-specific rescue groups to evaluate the effectiveness of AYRADIA oral suspension to treat dogs naturally infected with *Giardia duodenalis*. Effectiveness was evaluated in 120 of the 180 dogs enrolled (80 in the AYRADIA oral suspension group and 40 in the control group). Dogs ranged in age from 5 weeks to 15.2 years old, weighed 2.0 and 37.2 kg (4.4 and 81.8 lbs), were of various pure or mixed breeds, and included intact, non-pregnant and non-lactating, or spayed females, and intact or neutered males.

Observations included baseline physical examination, body weight, hematology, serum chemistry, and urinalysis before and after treatment. In addition, three daily fecal samples before and three daily fecal after treatment were obtained for immunofluorescence assay (IFA) cyst counts. Safety was monitored during the study by documentation of adverse events (see **Adverse Reactions**).

The difference between AYRADIA oral suspension and the vehicle control in terms of post-treatment cyst counts was significantly different (p<0.001) and in favor of the AYRADIA-treated dogs. Additionally, there was a 99.9% percent reduction in cyst counts between baseline and post-treatment in the AYRADIA-treated group. Based on these results, AYRADIA oral suspension was demonstrated to be effective for the treatment of *Giardia duodenalis* in naturally infected dogs.

Target Animal Safety
In a laboratory safety study, 12-week old, healthy, Beagle puppies (4/sex/group) were administered AYRADIA oral suspension at 0X, 1X, 2X and 3X the therapeutic dose (25 mg/kg twice per day) for 15 days (3X the treatment duration) and at 5X the therapeutic dose for 5 days (the treatment duration). AYRADIA oral suspension at 5X the therapeutic dose was associated with self-limiting episodes of diarrhea and erythema of the ears. No other clinically relevant observations were noted during the study.

In a four-dog laboratory tolerance study, two dogs, approximately four months old, received an investigational metronidazole oral suspension formulation (160 mg/mL) at 500 mg/kg/day (10X the intended daily dose) for 7 days, and two dogs (one 12 months old and one 21 months old) received a commercially-available metronidazole tablet at 250 mg/kg/day (5X the intended daily dose) for 7 days. No abnormal clinical signs were observed in dogs treated at 250 mg/kg/day with the metronidazole tablet. The two dogs that received the metronidazole oral suspension at 500 mg/kg/day exhibited severe neurologic signs by Days 7 and 8, respectively. Ataxia and lack of ocular reflexes were observed in both dogs. Additional adverse signs in one of the dogs included lateral movements of head and eyes, recumbency, tremors, and mydriasis. The dogs recovered after cessation of metronidazole administration and treatment with repeated doses of diazepam and furosemide. Both dogs recovered fully within approximately 24 hours.

Storage Conditions
Store below 86°F (30°C) in the upright position.
Once opened, use within 6 months.

How Supplied
AYRADIA™ (metronidazole oral suspension) for dogs is supplied in bottle sizes of 30 mL and 100 mL oral suspension. Bottles come pre-assembled with a dispensing system and a 3 mL syringe is included in each carton.

Approved by FDA under NADA # 141-572

Manufactured for:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161
1-800-338-3659
us.virbac.com

Rev. 07/2023

Scan to view an instructional video on using the dispensing system.

Approved by FDA under NADA # 065-492

BIOMOX®
(amoxicillin tablets)
For use in DOGS only.

DESCRIPTION:
BIOMOX tablets are a broad-spectrum, semisynthetic antibiotic which provides bactericidal activity against a wide range of common gram-positive and gram-negative pathogens. Amoxicillin chemically is D-(-)α-amino-p-hydroxybenzyl penicillin trihydrate.

Inactive Ingredients:
Dibasic Calcium Phosphate Dihydrate, Magnesium Stearate, Microcrystalline Cellulose and Sodium Starch Glycolate.

ACTION:
Amoxicillin has bactericidal activity against susceptible organisms similar to that of ampicillin. It acts by inhibiting the biosynthesis of bacterial cell wall mucopeptides. Most strains of the following gram-positive and gram-negative bacteria have demonstrated susceptibility to amoxicillin, both *in vitro* and *in vivo*: nonpenicillinase-producing staphylococci, alpha- and beta-hemolytic streptococci, *Enterococcus faecalis*, *Escherichia coli* and *Proteus mirabilis*. Amoxicillin does not resist destruction by penicillinase; therefore, it is not effective against penicillinase-producing bacteria, particularly resistant staphylococci. Most strains of *Enterobacter* and *Klebsiella* and all strains of *Pseudomonas* are resistant. Amoxicillin may be given without regard to meals because it is stable in gastric acid. It is rapidly absorbed following oral administration and diffuses readily into most body fluids and tissues. It diffuses poorly into the brain and spinal fluid except when the meninges are inflamed. Most of the amoxicillin is excreted in the urine unchanged.

INDICATIONS:
BIOMOX® (amoxicillin tablets) are indicated for treatment of the following infections in dogs when caused by susceptible strains of organisms:

BACTERIAL DERMATITIS due to *Staphylococcus aureus*, *Streptococcus* spp., *Staphylococcus* spp., and *Escherichia coli*.

SOFT TISSUE INFECTIONS
(abscesses, wounds, lacerations) due to *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus* spp.

With all antibiotic therapy, appropriate *in vitro* cultures and sensitivities should be conducted prior to treatment.

CONTRAINDICATIONS:
Use of amoxicillin is contraindicated in animals with a history of an allergic reaction to penicillin.

ADVERSE REACTIONS:
Amoxicillin is a semisynthetic penicillin and, therefore, has the potential for producing allergic reactions. Epinephrine and/or steroids should be administered if an allergic reaction occurs.

WARNINGS:
For use in dogs only.

PRECAUTIONS:
Until adequate reproductive studies are accomplished, BIOMOX® (amoxicillin tablets) should not be used in pregnant or breeding animals.

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

DOSAGE AND ADMINISTRATION:
The recommended dosage is 5 mg per pound of body weight administered twice daily for 5 to 7 days or 48 hours after all clinical signs have subsided. If no improvement is noted in 5 days, the diagnosis should be reconsidered and therapy changed.

SUPPLY:
BIOMOX® (amoxicillin tablets) are supplied in 50 mg, 100 mg and 200 mg concentrations in bottles of 500 tablets.

Manufactured for:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161
1-800-338-3659

Printed in USA
Rev. -06 for 50 mg and 100 mg; Rev. -07 for 200 mg
05/23

See productdata.aphis.usda.gov for a summary of the studies approved by the USDA for licensing this product. This package insert also contains additional information developed by the licensee.

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza$_3$-Respiratory Syncytial Virus Vaccine Modified Live Virus

BOVIGEN™ Platinum 5

CONTENTS:
Infectious Bovine Rhinotracheitis Virus (IBR), Modified Live Virus
Bovine Virus Diarrhea Virus (BVD), Modified Live Virus
Bovine Parainfluenza$_3$ Virus (PI$_3$), Modified Live Virus
Bovine Respiratory Syncytial Virus Vaccine (BRSV), Modified Live Virus

INDICATIONS: This product has been shown to be effective for the vaccination of healthy cattle against infectious bovine rhinotracheitis virus (IBR), bovine virus diarrhea virus Type I (BVD), bovine virus diarrhea virus Type II (BVD), bovine parainfluenza$_3$ virus (PI$_3$), and bovine respiratory syncytial virus (BRSV). The duration of immunity has not been determined. This product was licensed prior to the requirement to establish a minimum age for use. For more information regarding efficacy and safety data, see productdata.aphis.usda.gov.

BOVIGEN Platinum 5 may be used with pregnant cows and calves nursing pregnant cows provided they were vaccinated, 30 to 60 days pre-breeding, with BOVIGEN Platinum 3, BOVIGEN Platinum 3 LP, BOVIGEN Platinum 5 or BOVIGEN Platinum 5 L5.

This product contains BVD Type I and BVD Type II.

DIRECTIONS AND DOSAGE: Rehydrate the desiccated vial with accompanying diluent and shake well. Inject 2 mL subcutaneously using aseptic technique, followed by a second dose of monovalent bovine respiratory syncytial virus vaccine (BOVIGEN Platinum BRSV) to be given 14 to 28 days after the first dose. The need for annual booster vaccinations has not been established for this product. The presence of maternal antibody is known to interfere with the development of active immunity in calves and additional boosters will be required in most young animals. For advice on revaccination frequency, consult your veterinarian. Do not mix with other products, except as specified on the label.

CAUTIONS: Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian. Failure to follow label directions may result in abortions. Store at 35-46°F (2-8°C). **DO NOT FREEZE.** Use entire contents when first opened. Do not vaccinate within 21 days of slaughter. In case of human exposure, contact a physician. Inactivate unused contents before disposal. Allergic reactions may follow the use of vaccines; **ANTIDOTE:** Epinephrine.

PRODUCT DESCRIPTION:
BOVIGEN Platinum 5 contains desiccated Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza$_3$-Respiratory Syncytial Virus Vaccine and a sterile diluent to use as a diluent. The five viral antigens are combined in the proper ratio, stabilized and desiccated.

DISEASE:
The viruses listed below are considered contributors to the respiratory disease complex of cattle. Multiple infections do occur, and secondary bacterial infections may exacerbate the disease signs.

Infectious Bovine Rhinotracheitis Virus
IBR is an acute upper respiratory disease. Signs of IBR may include elevated temperature, hyperpnea, dyspnea, excessive nasal and ocular discharge, rapid breathing, cough and depression. Reproductive problems including abortions have been observed.

Bovine Virus Diarrhea Virus
BVD is often obscured or confused with other conditions of the respiratory disease complex. Clinical signs may include fever, anorexia, coughing, depression, diarrhea, and occasional lameness. BVD may be inapparent, chronic, or a fatal mucosal disease.

BVD may cause suppression of the immune system. Affected animals have increased susceptibility to secondary infections. BVD in pregnant animals may cause abortions or malformed and weak calves at birth. Chronic disease with erosions in the alimentary tract is referred to as "Mucosal Disease" and is usually fatal.

Bovine Parainfluenza$_3$ Virus
Parainfluenza$_3$ infections may cause few noticeable signs. Disease signs caused by PI$_3$ virus generally appear within 14 days after shipment and arrival of calves at their destination. Signs are weakness, depression, watery to mucopurulent nasal discharge, fever, coughing, and weight loss. PI$_3$ is a contributor to the Bovine Respiratory Disease Complex.

Bovine Respiratory Syncytial Virus
BRSV infections occur in dairy and beef cattle of all ages, including nursing calves. BRSV signs follow an incubation of 5 to 7 days. Infected calves and adult animals exhibit signs of acute respiratory disease that may include fever, cough, rapid breathing, subcutaneous edema of the throat, subcutaneous emphysema of the neck, depression, nasal depression, nasal discharge, ocular discharge, anorexia, hyperpnea, pulmonary edema and emphysema. BRSV may predispose cattle to secondary infections, particularly bacterial pneumonia. In an acute outbreak, sudden death has been reported. Enzootic pneumonia of dairy calves associated with BRSV may occur at 10 days of age. BRSV signs vary in severity but may rapidly progress to a crisis phase.

Recovery of adult animals is rapid and usually uneventful. Diagnosis is difficult in the field and laboratory. After the animal exhibits signs of disease, the virus usually is not isolated. Paired serum samples may assist in determining existing herd infections.

IMMUNE RESPONSES:
Research demonstrated BOVIGEN Platinum 5 is safe and efficacious; however, individual animals may be unable to develop an adequate immune response following vaccination due to concurrent disease, malnutrition, parasitism, or stress due to shipment or environmental conditions. For more information on revaccination in the face of stress or an exposure, contact your veterinarian.

SAFETY:
Safety in pregnant heifers and cows was demonstrated in trials conducted at three separate sites. The heifers and cows were vaccinated prior to breeding with BOVIGEN Platinum 5 L5, followed by a post-breeding vaccination at the first, second or third trimester of pregnancy. The cows were observed from pregnancy vaccination through calving for fetal loss. Heifers and cows vaccinated with BOVIGEN Platinum 5 L5 had abortions and calving rates similar to the control cows.

Calving Rates (normal calves delivered/total deliveries)

Trimester	Vaccinates	Controls
1	200/208 (96%)	205/213 (96%)
2	302/313 (96%)	293/308 (95%)
3	193/205 (94%)	195/208 (94%)
Total	695/726 (96%)	693/729 (95%)

The fetal loss in the two groups was similar with 4% in the BOVIGEN Platinum 5 L5 vaccinated groups and 5% in the control groups. Following calving, each calf's health was monitored for 4 weeks. The health of the calves in the BOVIGEN Platinum 5 L5 vaccinated dams was similar to the health of calves born to the control dams.
WARNING: Fetal health risks associated with vaccination of pregnant animals with modified live virus vaccines cannot be unequivocally determined by clinical trials conducted for licensure. Vaccination of pregnant animals with modified live vaccines should be discussed with a veterinarian.

FOR VETERINARY USE ONLY

SUPPLIED:
10 dose (20 mL) 50 per case
50 dose (100 mL) 20 per case

Manufactured by:
Diamond Animal Health, Inc.
Des Moines, IA 50327 U.S.A.
U.S. Veterinary License No. 213
Product Code No.: 1181.20

Distributed by:
Virbac AH, Inc.
Fort Worth, TX 76161
1-800-338-3659

Rev. 01/24
02351

PRODUCT INSERTS/DISCLOSURES

See productdata.aphis.usda.gov for a summary of the studies approved by the USDA for licensing this product. This package insert also contains additional information developed by the licensee.

Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza$_3$-Respiratory Syncytial Virus Vaccine Modified Live Virus Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae-Pomona Bacterin

BOVIGEN™ Platinum 5 L5

CONTENTS:
Infectious Bovine Rhinotracheitis Virus (IBR), Modified Live Virus
Bovine Virus Diarrhea Virus (BVD), Modified Live Virus
Bovine Parainfluenza$_3$ Virus (PI$_3$), Modified Live Virus
Bovine Respiratory Syncytial Virus Vaccine (BRSV), Modified Live Virus
Leptospira Canicola
Leptospira Grippotyphosa
Leptospira Hardjo
Leptospira Icterohaemorrhagiae
Leptospira Pomona

INDICATIONS: This product has been shown to be effective for the vaccination of healthy cattle against infectious bovine rhinotracheitis virus (IBR), bovine virus diarrhea virus Type I (BVD), bovine virus diarrhea virus Type II (BVD), bovine parainfluenza$_3$ virus (PI$_3$), bovine respiratory syncytial virus (BRSV) and *Leptospira borgpetersenii* serovar *hardjo-bovis* and *Leptospira canicola-grippotyphosa-hardjo-icterohaemorrhagiae-pomona*. The duration of immunity has not been determined. This product was licensed prior to the requirement to establish a minimum age for use. For more information regarding efficacy and safety data, see productdata.aphis.usda.gov.

BOVIGEN Platinum 5 L5 may be used with pregnant cows and calves nursing pregnant cows provided they were vaccinated, 30 to 60 days pre-breeding, with BOVIGEN Platinum 3, BOVIGEN Platinum 3 LP, BOVIGEN Platinum 5 or BOVIGEN Platinum 5 L5.

This product contains BVD Type I and BVD Type II.

DIRECTIONS AND DOSAGE: Rehydrate the desiccated vial with accompanying diluent and shake well. Inject 2 mL subcutaneously using aseptic technique, followed by a second dose of monovalent bovine respiratory syncytial virus vaccine (BOVIGEN Platinum BRSV) to be given 14 to 28 days after the first dose. The need for annual booster vaccinations has not been established for this product. The presence of maternal antibody is known to interfere with the development of active immunity in calves and additional boosters will be required in most young animals. For advice on revaccination frequency, consult your veterinarian. Do not mix with other products, except as specified on the label.

CAUTIONS: Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian. Failure to follow label directions may result in abortions. Store at 35 - 46°F (2 - 8°C). **DO NOT FREEZE.** Use entire contents when first opened. Do not vaccinate within 21 days of slaughter. In case of human exposure, contact a physician. Inactivate unused contents before disposal. Allergic reactions may follow the use of vaccines; **ANTIDOTE:** Epinephrine. Contains thimerosal as a preservative.

PRODUCT DESCRIPTION:
BOVIGEN Platinum 5 L5 contains desiccated Bovine Rhinotracheitis-Virus Diarrhea-Parainfluenza$_3$- Respiratory Syncytial Virus Vaccine and a bacterin diluent. The five viral antigens are combined in the proper ratio, stabilized and desiccated into one cake. The desiccated viral fractions are rehydrated for use with a specially processed liquid Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae- Pomona Bacterin (Lepto 5).

DISEASE:
The viruses listed below are considered contributors to the respiratory disease complex of cattle. Multiple infections do occur, and secondary bacterial infections may exacerbate the disease signs.

Infectious Bovine Rhinotracheitis Virus
IBR is an acute upper respiratory disease. Signs of IBR may include elevated temperature, hyperpnea, dyspnea, excessive nasal and ocular discharge, rapid breathing, cough and depression. Reproductive problems including abortions have been observed.

Bovine Virus Diarrhea Virus
BVD is often obscured or confused with other conditions of the respiratory disease complex. Clinical signs may include fever, anorexia, coughing, depression, diarrhea, and occasional lameness. BVD may be inapparent, chronic, or a fatal mucosal disease. BVD may cause suppression of the immune system. Affected animals have increased susceptibility to secondary infections. BVD in pregnant animals may cause abortions or malformed and weak calves at birth. Chronic disease with erosions in the alimentary tract is referred to as "Mucosal Disease" and is usually fatal.

Bovine Parainfluenza$_3$ Virus
Parainfluenza$_3$ infections may cause few noticeable signs. Disease signs caused by PI$_3$ virus generally appear within 14 days after shipment and arrival of calves at their destination. Signs are weakness, depression, watery to mucopurulent nasal discharge, fever, coughing, and weight loss. PI$_3$ is a contributor to the Bovine Respiratory Disease Complex.

Bovine Respiratory Syncytial Virus
BRSV infections occur in dairy and beef cattle of all ages, including nursing calves. BRSV signs follow an incubation of 5 to 7 days. Infected calves and adult animals exhibit signs of acute respiratory disease that may include fever, cough, rapid breathing, subcutaneous edema of the throat, subcutaneous emphysema of the neck, depression, nasal discharge, ocular discharge, anorexia, hyperpnea, pulmonary edema and emphysema. BRSV may predispose cattle to secondary infections, particularly bacterial pneumonia. In an acute outbreak, sudden death has been reported. Enzootic pneumonia of dairy calves associated with BRSV may occur at 10 days of age. BRSV signs vary in severity but may rapidly progress to a crisis phase. Recovery of adult animals is rapid and usually uneventful. Diagnosis is difficult both in the field and laboratory. After the animal exhibits signs of disease, the virus usually is not isolated. Paired serum samples may assist in determining existing herd infections.

Leptospira Canicola-Grippotyphosa-Hardjo-Icterohaemorrhagiae-Pomona
Leptospirosis is widespread in the animal population of the United States and is considered one of the most infectious diseases of farm animals.

Man can become infected either from animals with the disease or from an infective environmental source. In animals, the disease is known to cause reproduction disorders, loss of weight, decreased milk production and sometimes death. The economic losses suffered are very large. The disease can be caused by several specific leptospires.

Five important serovars have been identified and are included in this product. Because specific serovar diagnosis is very difficult, and also due to the widespread nature of potential infection, it is recommended that all animals be vaccinated before introduction into the concentrated holding areas currently utilized on many premises. When infection is diagnosed, it is advisable to separate those animals showing disease signs and to vaccinate the remainder of the herd with Lepto 5 alone. The apparent effectiveness of Lepto 5 will depend upon the number of animals exposed and incubating the disease at the time of vaccination. Vaccination cannot be expected to protect animals already in the incubating stages of the disease.

Serologic studies indicate widespread distribution of all these causative agents.

IMMUNE RESPONSES:
Research demonstrated BOVIGEN Platinum 5 L5 is safe and efficacious; however, individual animals may be unable to develop an adequate immune response following vaccination due to concurrent disease, malnutrition, parasitism, or stress due to shipment or environmental conditions. For more information on revaccination in the face of stress or an exposure, contact your veterinarian.

SAFETY:
Safety in pregnant heifers and cows was demonstrated in trials conducted at three separate sites. The heifers and cows were vaccinated prior to breeding with BOVIGEN Platinum 5 L5, followed by a post-breeding vaccination at the first, second or third trimester of pregnancy. The cows were observed from pregnancy vaccination through calving for fetal loss. Heifers and cows vaccinated with BOVIGEN Platinum 5 L5 had abortions and calving rates similar to the control cows.

Calving Rates (normal calves delivered/total deliveries)

Trimester	Vaccinates	Controls
1	200/208 (96%)	205/213 (96%)
2	302/313 (96%)	293/308 (95%)
3	193/205 (94%)	195/208 (94%)
Total	695/726 (96%)	693/729 (95%)

The fetal loss in the two groups was similar with 4% in the BOVIGEN Platinum 5 L5 vaccinated groups and 5% in the control groups. Following calving, each calf's health was monitored for 4 weeks. The health of the calves in the BOVIGEN Platinum 5 L5 vaccinated dams was similar to the health of calves born to the control dams. **WARNING:** Fetal health risks associated with vaccination of pregnant animals with modified live virus vaccines cannot be unequivocally determined by clinical trials conducted for licensure. Vaccination of pregnant animals with modified live vaccines should be discussed with a veterinarian.

FOR VETERINARY USE ONLY

SUPPLIED:
10 dose (20 mL) 50 per case
50 dose (100 mL) 20 per case

Manufactured by:
Diamond Animal Health, Inc.
Des Moines, IA 50327 U.S.A.
U.S. Veterinary License No. 213
Product Code No.: 4461.20

Distributed by:
Virbac AH, Inc.
Fort Worth, TX 76161
1-800-338-3659

Rev. 01/24
02352

See productdata.aphis.usda.gov for a summary of the studies approved by the USDA for licensing this product. This document also contains additional information developed by the licensee.

Bovine Rhinotracheitis-Virus Diarrhea Vaccine
Modified Live Virus

BOVIGEN™ Platinum 3

CONTENTS:
Infectious Bovine Rhinotracheitis Virus (IBR), Modified Live Virus
Bovine Virus Diarrhea Virus (BVD), Modified Live Virus

INDICATIONS: This product has been shown to be effective for the vaccination of healthy cattle against infectious bovine rhinotracheitis virus (IBR), bovine virus diarrhea virus Type I (BDV), and bovine virus diarrhea virus Type II (BVD). The duration of immunity has not been determined. This product was licensed prior to the requirement to establish a minimum age for use. For more information regarding efficacy and safety data, see productdata.aphis.usda.gov.

BOVIGEN Platinum 3 may be used in pregnant cows and calves nursing pregnant cows provided they were vaccinated, 30 to 60 days pre-breeding, with BOVIGEN Platinum 3, BOVIGEN Platinum 3 LP, BOVIGEN Platinum 5, or BOVIGEN Platinum 5 L5.

This product contains BVD Type I and BVD Type II.

DIRECTIONS AND DOSAGE: Rehydrate the desiccated vial with accompanying diluent and shake well. Inject 2 mL subcutaneously using aseptic technique. The need for annual booster vaccinations has not been established for this product. The presence of maternal antibody is known to interfere with the development of active immunity in calves and additional boosters will be required in most young animals. For advice on revaccination frequency, consult your veterinarian. Do not mix with other products, except as specified on the label.

CAUTION: Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian. Failure to follow label direction may result in abortions. Store at 35-46°F (2-8°C). **DO NOT FREEZE**. Use entire contents when first opened. Do not vaccinate within 21 days of slaughter. In case of human exposure, contact a physician. Inactivate unused contents before disposal. Allergic reactions may follow the use of vaccines; **ANTIDOTE**: Epinephrine.

PRODUCT DESCRIPTION:
BOVIGEN Platinum 3 contains desiccated Bovine Rhinotracheitis-Virus Vaccine and a sterile diluent to use as a diluent. The three viral antigens are combined in the proper ratio, stabilized and desiccated.

DISEASE:
The viruses listed below are considered contributors to the respiratory disease complex of cattle. Multiple infections do occur, and secondary bacterial infections may exacerbate the disease signs.

Infectious Bovine Rhinotracheitis Virus
IBR is an acute upper respiratory disease. Signs of IBR may include elevated temperature, hyperpnea, dyspnea, excessive nasal and ocular discharge, rapid breathing, cough and depression. Reproductive problems including abortions have been observed.

Bovine Virus Diarrhea Virus
BVD is often obscured or confused with other conditions of the respiratory disease complex. Clinical signs may include fever, anorexia, coughing, depression, diarrhea, and occasional lameness. BVD may be inapparent, chronic, or a fatal mucosal disease.

BVD may cause suppression of the immune system. Affected animals have increased susceptibility to secondary infections. BVD in pregnant animals may cause abortions or malformed and weak calves at birth. Chronic disease with erosions in the alimentary tract is referred to as "Mucosal Disease" and is usually fatal.

IMMUNE RESPONSES:
Research demonstrated BOVIGEN Platinum 3 is safe and efficacious; however, individual animals may be unable to develop an adequate immune response following vaccination due to concurrent disease, malnutrition, parasitism, or stress due to shipment or environmental conditions. For more information on revaccination in the face of stress or an exposure, contact your veterinarian.

SAFETY:
Safety in pregnant heifers and cows was demonstrated in trials conducted at three separate sites. The heifers and cows were vaccinated prior to breeding with BOVIGEN Platinum 5 L5, followed by a post-breeding vaccination at the first, second or third trimester of pregnancy. The cows were observed from pregnancy vaccination through calving for fetal loss. Heifers and cows vaccinated with BOVIGEN Platinum 5 L5 had abortions and calving rates similar to the control cows.

Calving Rates (normal calves delivered/total deliveries)

Trimester	Vaccinates	Controls
1	200/208 (96%)	205/213 (96%)
2	302/313 (96%)	293/308 (95%)
3	193/205 (94%)	195/208 (94%)
Total	695/726 (96%)	693/729 (95%)

The fetal loss in the two groups was similar with 4% in the BOVIGEN Platinum 5 L5 vaccinated groups and 5% in the control groups. Following calving, each calf's health was monitored for 4 weeks. The health of the calves in the BOVIGEN Platinum 5 L5 vaccinated dams was similar to the health of calves born to the control dams.

WARNING: Fetal health risks associated with vaccination of pregnant animals with modified live virus vaccines cannot be unequivocally determined by clinical trials conducted for licensure. Vaccination of pregnant animals with modified live vaccines should be discussed with a veterinarian.

FOR VETERINARY USE ONLY

SUPPLIED:
10 dose (20 mL) 50 per case
50 dose (100 mL) 20 per case

Manufactured by:
Diamond Animal Health, Inc.
Des Moines, IA 50327 U.S.A.
U.S. Veterinary License No. 213
Product Code No.: 1151.20

Distributed by:
Virbac AH, Inc.
Fort Worth, TX 76161
1-800-338-3659

Rev. 01 002BP3-0125
66730, 66731

DIAMOND®

Virbac

PRODUCT INSERTS/DISCLOSURES

See productdata.aphis.usda.gov for a summary of the studies approved by the USDA for licensing this product. This document also contains additional information developed by the licensee.

Bovine Rhinotracheitis-Virus Diarrhea Vaccine
Modified Live Virus
Leptospira Pomona Bacterin

BOVIGEN™ Platinum 3 LP

CONTENTS:
Infectious Bovine Rhinotracheitis Virus (IBR), Modified Live Virus
Bovine Virus Diarrhea Virus (BVD), Modified Live Virus
Leptospira Pomona

INDICATIONS: This product has been shown to be effective for the vaccination of healthy cattle against infectious bovine rhinotracheitis virus (IBR), bovine virus diarrhea virus Type I (BDV), bovine virus diarrhea virus Type II (BVD) and *Leptospira pomona*. The duration of immunity has not been determined. This product was licensed prior to the requirement to establish a minimum age for use. For more information regarding efficacy and safety data, see productdata.aphis.usda.gov.

BOVIGEN Platinum 3 LP may be used in pregnant cows and calves nursing pregnant cows provided they were vaccinated, 30 to 60 days pre-breeding, with BOVIGEN Platinum 3, BOVIGEN Platinum 3 LP, BOVIGEN Platinum 5, or BOVIGEN Platinum 5 L5.

This product contains BVD Type I and BVD Type II.

DIRECTIONS AND DOSAGE: Rehydrate the desiccated vial with accompanying diluent and shake well. Inject 2 mL subcutaneously using aseptic technique. The need for annual booster vaccinations has not been established for this product. The presence of maternal antibody is known to interfere with the development of active immunity in calves and additional boosters will be required in most young animals. For advice on revaccination frequency, consult your veterinarian. Do not mix with other products, except as specified on the label.

CAUTION: Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian. Failure to follow label direction may result in abortions. Store at 35-46°F (2-8°C). **DO NOT FREEZE**. Use entire contents when first opened. Do not vaccinate within 21 days of slaughter. In case of human exposure, contact a physician. Inactivate unused contents before disposal. Allergic reactions may follow the use of vaccines; **ANTIDOTE**: Epinephrine. Contains thimerosal as a preservative.

PRODUCT DESCRIPTION:
BOVIGEN Platinum 3 LP contains desiccated Bovine Rhinotracheitis-Virus Diarrhea Vaccine and a bacterin diluent. The three viral antigens are combined in the proper ratio, stabilized and desiccated into one cake. The desiccated viral fractions are rehydrated for use with a specially processed liquid Leptospira Pomona Bacterin (LP).

DISEASE:
The viruses listed below are considered contributors to the respiratory disease complex of cattle. Multiple infections do occur, and secondary bacterial infections may exacerbate the disease signs.

Infectious Bovine Rhinotracheitis Virus
IBR is an acute upper respiratory disease. Signs of IBR may include elevated temperature, hyperpnea, dyspnea, excessive nasal and ocular discharge, rapid breathing, cough and depression. Reproductive problems including abortions have been observed.

Bovine Virus Diarrhea Virus
BVD is often obscured or confused with other conditions of the respiratory disease complex. Clinical signs may include fever, anorexia, coughing, depression, diarrhea, and occasional lameness. BVD may be inapparent, chronic, or a fatal mucosal disease. BVD may cause suppression of the immune system. Affected animals have increased susceptibility to secondary infections. BVD in pregnant animals may cause abortions or malformed and weak calves at birth. Chronic disease with erosions in the alimentary tract is referred to as "Mucosal Disease" and is usually fatal.

Leptospira Pomona
Leptospirosis is widespread in the animal population of the United States and is considered one of the most infectious diseases of farm animals.

Man can become infected either from animals with the disease or from an infective environmental source. In animals, the disease is known to cause reproduction disorders, loss of weight, decreased milk production and sometimes death. The economic losses suffered are very large. The disease can be caused by several specific leptospires.

IMMUNE RESPONSES:
Research demonstrated BOVIGEN Platinum 3 LP is safe and efficacious; however, individual animals may be unable to develop an adequate immune response following vaccination due to concurrent disease, malnutrition, parasitism, or stress due to shipment or environmental conditions. For more information on revaccination in the face of stress or an exposure, contact your veterinarian.

SAFETY:
Safety in pregnant heifers and cows was demonstrated in trials conducted at three separate sites. The heifers and cows were vaccinated prior to breeding with BOVIGEN Platinum 5 L5, followed by a post-breeding vaccination at the first, second or third trimester of pregnancy. The cows were observed from pregnancy vaccination through calving for fetal loss. Heifers and cows vaccinated with BOVIGEN Platinum 5 L5 had abortions and calving rates similar to the control cows.

Calving Rates (normal calves delivered/total deliveries)

Trimester	Vaccinates	Controls
1	200/208 (96%)	205/213 (96%)
2	302/313 (96%)	293/308 (95%)
3	193/205 (94%)	195/208 (94%)
Total	695/726 (96%)	693/729 (95%)

The fetal loss in the two groups was similar with 4% in the BOVIGEN Platinum 5 L5 vaccinated groups and 5% in the control groups. Following calving, each calf's health was monitored for 4 weeks. The health of the calves in the BOVIGEN Platinum 5 L5 vaccinated dams was similar to the health of calves born to the control dams.

WARNING: Fetal health risks associated with vaccination of pregnant animals with modified live virus vaccines cannot be unequivocally determined by clinical trials conducted for licensure. Vaccination of pregnant animals with modified live vaccines should be discussed with a veterinarian.

FOR VETERINARY USE ONLY

SUPPLIED:
10 dose (20 mL) 50 per case
50 dose (100 mL) 20 per case

Manufactured by:
Diamond Animal Health, Inc.
Des Moines, IA 50327 U.S.A.
U.S. Veterinary License No. 213
Product Code No.: 4389.21

Distributed by:
Virbac AH, Inc.
Fort Worth, TX 76161
1-800-338-3659

Rev. 01 002BP3LP-0125
66732, 66733

DIAMOND®

Virbac

Virbac

CLINTABS®
(clindamycin hydrochloride tablets)

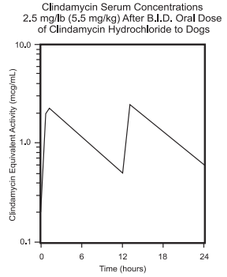
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
CLINTABS® tablets contain clindamycin hydrochloride which is the hydrated salt of clindamycin. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chlorosubstitution of the 7(R)-hydroxyl group of a naturally produced antibiotic produced by *Streptomyces lincolnensis var. lincolnensis*.

CLINTABS tablets (For Use in Dogs Only):
25 mg Tablet, each white bisected tablet is marked "C" above the bisect and "25" below the bisect and contains clindamycin hydrochloride equivalent to 25 mg of clindamycin.
75 mg Tablet, each white bisected tablet is marked "C" above the bisect and "75" below the bisect and contains clindamycin hydrochloride equivalent to 75 mg of clindamycin.
150 mg Tablet, each white tablet is marked "C 150" on one side and contains clindamycin hydrochloride equivalent to 150 mg of clindamycin.

CLINICAL PHARMACOLOGY
Absorption: Clindamycin hydrochloride is rapidly absorbed from the canine gastrointestinal tract.

Dog Serum Levels: Serum levels at or above 0.5 µg/mL can be maintained by oral dosing at a rate of 2.5 mg/lb of clindamycin hydrochloride every 12 hours. This same study revealed that average peak serum concentrations of clindamycin occur 1 hour and 15 minutes after oral dosing. The elimination half-life for clindamycin in dog serum was approximately 5 hours. There was no bioactivity accumulation after a regimen of multiple oral doses in healthy dogs.



Metabolism and Excretion: Extensive studies of the metabolism and excretion of clindamycin hydrochloride administered orally in animals and humans have shown that unchanged drug and bioactive and bioinactive metabolites are excreted in urine and feces. Almost all of the bioactivity detected in serum after clindamycin hydrochloride administration is due to the parent molecule (clindamycin). Urine bioactivity, however, reflects a mixture of clindamycin and active metabolites, especially N-demethyl clindamycin and clindamycin sulfoxide.

Site and Mode of Action: Clindamycin is an inhibitor of protein synthesis in the bacterial cell. The site of binding appears to be in the 50S sub-unit of the ribosome. Binding occurs to the soluble RNA fraction of certain ribosomes, thereby inhibiting the binding of amino acids to those ribosomes. Clindamycin differs from cell wall inhibitors in that it causes irreversible modification of the protein-synthesizing subcellular elements at the ribosomal level.

Microbiology: Clindamycin is a lincosaminide antimicrobial agent with activity against a wide variety of aerobic and anaerobic bacterial pathogens. Clindamycin is a bacteriostatic compound that inhibits bacterial protein synthesis by binding to the 50S ribosomal sub-unit. The minimum inhibitory concentrations (MICs) of Gram-positive and obligate anaerobic pathogens isolated from dogs in the United States are presented in Table 1. Bacteria were isolated in 1998-1999. All MICs were performed in accordance with the Clinical and Laboratory Standards Institute (CLSI).

Table 1. Clindamycin MIC Values (µg/mL) from Diagnostic Laboratory Survey Data Evaluating Canine Pathogens in the U.S. during 1998-99[1]

Organism	Number of Isolates	MIC_{50}	MIC_{85}	MIC_{90}	Range
Soft Tissue/Wound[2]					
Staphylococcus aureus	17	0.5	0.5	≥4.0	0.25-≥4.0
Staphylococcus intermedius	28	0.25	0.5	≥4.0	0.125-≥4.0
Staphylococcus spp.	18	0.5	0.5	≥4.0	0.25-≥4.0
Beta-hemolytic streptococci	46	0.5	0.5	≥4.0	0.25-≥4.0
Streptococcus spp.	11	0.5	≥4.0	≥4.0	0.25-≥4.0
Osteomyelitis/Bone[3]					
Staphylococcus aureus	20	0.5	0.5	0.5	0.5[4]
Staphylococcus intermedius	15	0.5	≥4.0	≥4.0	0.25-≥4.0
Staphylococcus spp.	18	0.5	≥4.0	≥4.0	0.25-≥4.0
Beta-hemolytic streptococci	21	0.5	2.0	2.0	0.25-≥4.0
Streptococcus spp.	21	≥4.0	≥4.0	≥4.0	0.25-≥4.0
Dermal/Skin[5]					
Staphylococcus aureus	25	0.5	≥4.0	≥4.0	0.25-≥4.0
Staphylococcus intermedius	48	0.5	≥4.0	≥4.0	0.125-≥4.0
Staphylococcus spp.	32	0.5	≥4.0	≥4.0	0.25-≥4.0
Beta-hemolytic streptococci	17	0.5	0.5	0.5	0.25-0.5

[1] The correlation between the *in vitro* susceptibility data and clinical response has not been determined.

[2] Soft Tissue/Wound: includes samples labeled wound, abscess, aspirate, exudates, draining tract, lesion, and mass

[3] Osteomyelitis/Bone: includes samples labeled bone, fracture, joint, tendon

[4] No range, all isolates yielded the same value

[5] Dermal/Skin: includes samples labeled skin, skin swab, biopsy, incision, lip

INDICATIONS
CLINTABS® (clindamycin hydrochloride tablets) (for use in dogs only) are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below:
Dogs: Skin infections (wounds and abscesses) due to coagulase positive staphylococci (*Staphylococcus aureus* or *Staphylococcus intermedius*). **Deep wounds and abscesses** due to *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum* and *Clostridium perfringens*.
Dental infections due to *Staphyloccus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum* and *Clostridium perfringens*. **Osteomyelitis** due to *Staphylococcus aureus*, *Bacteroides fragilis*, *Prevotella melaninogenicus*, *Fusobacterium necrophorum* and *Clostridium perfringens*.

CONTRAINDICATIONS
CLINTABS tablets are contraindicated in animals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

Because of potential adverse gastrointestinal effects, do not administer to rabbits, hamsters, guinea pigs, horses, chinchillas or ruminating animals.

WARNINGS
Keep out of reach of children. Not for human use.

Keep CLINTABS tablets in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS
During prolonged therapy of one month or greater, periodic liver and kidney function tests and blood counts should be performed.

The use of clindamycin hydrochloride occasionally results in overgrowth of non-susceptible organisms such as clostridia and yeasts. Therefore, the administration of CLINTABS tablets should be avoided in those species sensitive to the gastrointestinal effects of clindamycin (see **CONTRAINDICATIONS**). Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Clindamycin hydrochloride has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, CLINTABS tablets should be used with caution in animals receiving such agents.

Safety in gestating bitches or breeding male dogs has not been established.

ADVERSE REACTIONS
Side effects occasionally observed in either clinical trials or during clinical use were vomiting and diarrhea.

To report adverse reactions or a suspected adverse reaction, call 1-800-338-3659.

DOSAGE AND ADMINISTRATION
Dogs:
Infected Wounds, Abscesses, and Dental Infections
Oral: 2.5-15.0 mg/lb body weight every 12 hours.
Duration: Treatment with clindamycin hydrochloride products may be continued up to a maximum of 28 days if clinical judgment indicates. Treatment of acute infections should not be continued for more than three or four days if no response to therapy is seen.

Dosage Schedule:
Tablets
CLINTABS 25 mg, administer 1-6 tablets every 12 hours for each 10 pounds of body weight.
CLINTABS 75 mg, administer 1-6 tablets every 12 hours for each 30 pounds of body weight.
CLINTABS 150 mg, administer 1-6 tablets every 12 hours for each 60 pounds of body weight.

Dogs:
Osteomyelitis
Oral: 5.0-15.0 mg/lb body weight every 12 hours.
Duration: Treatment with clindamycin hydrochloride is recommended for a minimum of 28 days. Treatment should not be continued for longer than 28 days if no response to therapy is seen.

Dosage Schedule:
Tablets
CLINTABS 25 mg, administer 2-6 tablets every 12 hours for each 10 pounds of body weight.
CLINTABS 75 mg, administer 2-6 tablets every 12 hours for each 30 pounds of body weight.
CLINTABS 150 mg, administer 2-6 tablets every 12 hours for each 60 pounds of body weight.

ANIMAL SAFETY SUMMARY
Rat and Dog Data: One year oral toxicity studies in rats and dogs at doses of 30, 100 and 300 mg/kg/day (13.6, 45.5 and 136.4 mg/lb/day) have shown clindamycin hydrochloride capsules to be well tolerated. Differences did not occur in the parameters evaluated to assess toxicity when comparing groups of treated animals with contemporary controls. Rats administered clindamycin hydrochloride at 600 mg/kg/day (272.7 mg/lb/day) for six months tolerated the drug well; however, dogs orally dosed at 600 mg/kg/day (272.7 mg/lb/day) vomited, had anorexia, and subsequently lost weight. At necropsy these dogs had erosive gastritis and focal areas of necrosis of the mucosa of the gall bladder.

Safety in gestating bitches or breeding males has not been established.

STORAGE
Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

HOW SUPPLIED
CLINTABS tablets are available as:
25 mg - bottles of 400
75 mg - bottles of 200
150 mg - bottles of 100

Approved by FDA under ANADA # 200-316

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. 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 for: Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161, USA
1-800-338-3659

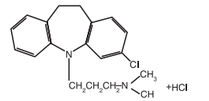
Revised: February 2023 301617-06

PRODUCT INSERTS/DISCLOSURES

CLOMICALM®
(clomipramine hydrochloride)

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

Description:
CLOMICALM® (clomipramine hydrochloride) tablets belong to the dibenzazepine class of tricyclic antidepressants. Clomipramine hydrochloride is 3-chloro-5[3-(dimethyl-amino)propyl]-10,11dihydro-5H-dibenz[b,f]azepine monohydrochloride. CLOMICALM tablets are oblong, light brown in color and contain clomipramine hydrochloride formulated together with meat components. The molecular weight of clomipramine hydrochloride is 351.3. The structural formula is:



Clinical Pharmacology:
Clomipramine hydrochloride reduces the clinical signs of separation anxiety by affecting serotonergic and noradrenergic neuronal transmission in the central nervous system. While clomipramine hydrochloride can cause lethargy in dogs (see Adverse Reactions) its mode of action is not as a sedative. Clomipramine hydrochloride's capacity to inhibit re-uptake of serotonin in the central nervous system is believed to be the primary mechanism of action. Clomipramine hydrochloride is rapidly absorbed when administered orally. A single-dose crossover study involving 12 dogs evaluated clomipramine hydrochloride bioavailability after IV (2 mg/kg) and oral (4 mg/kg) administration in either a fed or fasted state. The administration of clomipramine hydrochloride in the presence of food resulted in an increase in the rate and extent of drug absorption as shown in the following table (mean ±SD):

	$AUC_{0\text{-}inf}$ (nmol hr/L)	Cmax (nmol/L)	Tmax (hr)	Absolute Bioavailability (F)
Fed	1670±575	601±286	1.18±0.32	0.21±0.07
Fasted	1350±447	379±154	1.31±0.32	0.17±0.05

The absolute bioavailability is approximately 25% greater in fed dogs. The apparent terminal plasma half-life ranges from approximately 2 to 9 hours in fed and 3 to 21 hours in fasted dogs. The difference and variability in apparent half-life estimates may be attributable to prolonged drug absorption in the fasted state. The relatively large volume of distribution (3.8±0.8 L/kg) suggests that the drug is widely distributed throughout the body. **Clomipramine is primarily metabolized in the liver.**

Indications and Usage: CLOMICALM tablets are to be used as part of a comprehensive behavioral management program to treat separation anxiety in dogs greater than 6 months of age. Inappropriate barking or destructive behavior, as well as inappropriate elimination (urination or defecation) may be alleviated by the use of CLOMICALM tablets in conjunction with behavior modification.

Separation anxiety is a complex behavior disorder displayed when the owner (or other attachment figure) leaves the dog. The signs of separation anxiety evaluated in controlled trials were vocalization, destructive behavior, excessive salivation, and inappropriate elimination. In the absence of the owner or attachment figure, dogs with separation anxiety may exhibit one or more of these clinical signs. Although the owner (attachment figure) may inadvertently misinterpret this behavior, which only happens in their absence, as spiteful, it is thought to be the result of anxiety experienced by the dog. Punishment is not considered appropriate for a dog with separation anxiety.

Proper recognition of clinical signs, including a complete patient history and assessment of the patient's household environment, is essential to accurately diagnose and treat separation anxiety.

The use of CLOMICALM tablets should not replace appropriate behavioral and environmental management but should be used to facilitate a comprehensive behavior management program.

Contraindications:
CLOMICALM tablets are contraindicated in dogs with known hypersensitivity to clomipramine or other tricyclic antidepressants.

CLOMICALM tablets should not be used in male breeding dogs. Testicular hypoplasia was seen in dogs treated for 1 year at 12.5 times the maximum daily dose.

CLOMICALM tablets should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor [e.g., selegiline hydrochloride (L-deprenyl), amitraz].

CLOMICALM tablets are contraindicated for use in dogs with a history of seizures or concomitantly with drugs which lower the seizure threshold.

Human Warnings:
Not for use in humans. Keep out of reach of children. In case of accidental ingestion seek medical attention immediately. In children, accidental ingestion should be regarded as serious. There is no specific antidote for clomipramine. Overdose in humans causes anticholinergic effects including effects on the central nervous (e.g., convulsions) and cardiovascular (e.g., arrhythmia, tachycardia) systems. People with known hypersensitivity to clomipramine should administer the product with caution.

Precautions:
General: CLOMICALM tablets are not recommended for other behavior problems, such as aggression (see Adverse Reactions). Studies to establish the safety and efficacy of CLOMICALM tablets in dogs less than 6 months of age have not been conducted.

Diagnosis: It is critical to conduct a comprehensive physical examination, including appropriate laboratory tests, and to obtain a thorough history and assessment of the patient's household environment, to rule-out causes of inappropriate behavior unrelated to separation anxiety before prescribing CLOMICALM tablets. Periodic reassessment of hematological and serum biochemical data during the administration of this medication is advised. Veterinarians should be familiar with the risks and benefits of the treatment of behavioral disorders in dogs before initiating therapy. Inappropriate use of CLOMICALM tablets, i.e., in the absence of a diagnosis or without concurrent behavioral modification, may expose the animal to unnecessary adverse effects and may not provide any lasting benefit of therapy.

Drug Interactions: Recommendations on the interaction between clomipramine and other medications are extrapolated from data generated in humans. Plasma levels of tricyclic antidepressants have been reported to be decreased by the concomitant administration of hepatic enzyme inducers (e.g., barbiturates, phenytoin); therefore plasma concentrations of clomipramine may be decreased by the concomitant administration of phenobarbital. Plasma levels of closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine). Tricyclic antidepressants themselves may exhibit hepatic enzyme inhibition and possibly increase plasma levels of barbiturates (phenobarbital). Caution is advised in using clomipramine with anticholinergic or sympathomimetic drugs or with other CNS-active drugs, including general anesthetics and neuroleptics.

Prior to elective surgery with general anesthetics, clomipramine should be discontinued for as long as clinically feasible.

Use in Concomitant Illness: Use with caution in dogs with cardiovascular disease. At 20 mg/kg/day (5X the maximum recommended dose), bradycardia and arrhythmias (atrioventricular node block and ventricular extrasystole) were observed in dogs. Because of its anticholinergic properties, clomipramine should be used with caution in patients with increased intraocular pressure, a history of narrow angle glaucoma, urinary retention or reduced gastrointestinal motility. Because clomipramine is principally metabolized in the liver, caution is advised in using this medication in the presence of preexisting liver disease.

Reproductive Safety: Safety studies to determine the effects of CLOMICALM tablets in pregnant or lactating female dogs have not been conducted. CLOMICALM tablets should not be used in breeding males (See Contraindications).

Efficacy:
Dose Establishment: A 12 week, placebo-controlled, multi-site clinical trial was conducted in the US and Europe to establish an effective dose of CLOMICALM tablets in dogs. Treatment with CLOMICALM tablets, at 2 - 4 mg/kg/day divided twice daily, in conjunction with behavioral modification (desensitization and counterconditioning) was more effective than behavior modification alone in reducing the signs of separation anxiety in dogs.

Dose Confirmation: In another placebo-controlled, multi-site clinical trial, CLOMICALM tablets at 2 - 4 mg/kg/day given either once daily or divided twice daily showed significant improvement in resolving signs of separation anxiety when tested against behavioral modification alone (desensitization and counterconditioning). In this 8 week study, the rate of improvement of the dogs receiving CLOMICALM tablets with behavioral modification was significantly faster than the rate of improvement of the dogs receiving behavioral modification alone. After one week on trial, 47% of the dogs receiving CLOMICALM tablets once or twice (divided dose) daily in conjunction with behavioral modification showed clinical improvement compared to improvement in 29% of the dogs receiving behavioral modification alone.

Safety:
CLOMICALM® (clomipramine hydrochloride) tablets were demonstrated to be well-tolerated in dogs at the recommended label dose of 2-4 mg/kg/day. In a six month target animal safety study, beagle dogs were dosed daily at 4 (1X), 12 (3X), and 20 (5X) mg/kg/day. Emesis was seen in all groups including the dogs receiving placebo, but occurred more frequently in dogs receiving 12 and 20 mg/kg. Decreased activity was also seen in dogs receiving the 12 and 20 mg/kg. There were no apparent treatment-related alterations in the following: body weights, physical examination findings, electrocardiograph examinations, hematology or biochemistry parameters, ophthalmoscopic examinations, macroscopic or microscopic organ examinations and organ weights. Average food and water consumption over the 26 week period was similar for control and treated groups. In a one year study, pure bred dogs were dosed daily at 12.5 (3X), 50 (12.5X), and 100 (25X) mg/kg/day. Emesis and mydriasis were observed within 15 minutes to one hour after dosing in dogs receiving 12.5, 50, and 100 mg/kg/day and lethargy was observed within 1 hour of dosing in dogs receiving 50 and 100 mg/kg. Testicular hypoplasia was seen in dogs receiving 50 mg/kg. At 100 mg/kg/day (25X) convulsions and eventual death occurred in five out of the eight dogs.

Adverse Reactions: Frequency and category of adverse reactions observed in dogs dosed with CLOMICALM tablets or placebo were observed in multisite clinical studies as follows.

Adverse Reactions Reported in Placebo-Controlled Clinical Field Trials

	CLOMICALM N=180	Placebo N=88
Emesis	36 (20%)	8 (9%)
Lethargy	26 (14%)	7 (8%)
Diarrhea	17 (9%)	4 (5%)
Polydipsia	6 (3%)	0
Decreased Appetite	6 (3%)	3 (3%)
Aggression*	3 (2%)	1 (1%)
Seizure	2 (1%)	0
Dry Mouth	1 (0.5%)	1 (1%)
Tremors	1 (0.5%)	0
Constipation	1 (0.5%)	0
Anisocoria	1 (0.5%)	0
Polyuria	1 (0.5%)	0
Hyperthermia	1 (0.5%)	0

*These dogs displayed growling behavior towards either humans or other dogs.

Post-Approval Experience: Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting: lethargy/depression, anorexia, elevation in liver enzymes, vomiting and diarrhea. Hepatobiliary disease has occurred, especially in the presence of pre-existing conditions or with concurrent administration of drugs metabolized via the hepatic system. Additionally, in an overdose situation, the following signs have been reported: ataxia, convulsion(s), anticholinergic effects (e.g., mydriasis, bradycardia, tachycardia, and arrhythmia) and vocalization.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

Dosage and Administration:
The recommended daily dose of CLOMICALM tablets is 2 to 4 mg/kg/day (0.9 -1.8 mg/lb/day) (see dosing table below). It can be administered as a single daily dose or divided twice daily based on patient response and/or tolerance of the side effects. It may be prudent to initiate treatment in divided doses to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop. To reduce the incidence of vomiting that may be experienced by some dogs, CLOMICALM tablets may be given with a small amount of food.

Dog Weight (lbs.)	CLOMICALM per Day	No. Tablets per Day	Tablet Strength
2.75-5.5	5 mg	1	5 mg
5.6-10.9	10 mg	2	5 mg
11-22	20 mg	1	20 mg
22.1-44	40 mg	1	40 mg
44.1-88	80 mg	1	80 mg
88.1-176	160 mg	2	80 mg

The specific methods of behavioral modification used in clinical trials involved desensitization and counterconditioning techniques. Since the manifestation of separation anxiety can vary according to the individual dog, it is advised that a specific behavior modification plan be developed based on a professional assessment of each individual case.

Once the desired clinical effect is achieved and the owners have successfully instituted the appropriate behavioral modification, the dose of CLOMICALM tablets may be reduced to maintain the desired effect or discontinued. Withdrawal side effects were not reported in studies with CLOMICALM tablets in dogs. However, in clinical practice, it is recommended to taper the individual patient dose while continuing to monitor the dog's behavior and clinical status through the dose reduction or withdrawal period. Continued behavioral modification is recommended to prevent recurrence of the clinical signs.

The effectiveness and clinical safety of CLOMICALM tablets for long-term use (i.e., for more than 12 weeks) has not been evaluated.

Professional judgment should be used in monitoring the patient's clinical status, response to therapy and tolerance to side effects to determine the need to continue treatment with CLOMICALM tablets and to continue to rule-out physiological disorders which may complicate the diagnosis and treatment of separation anxiety.

Storage Conditions: Store in a dry place at controlled room temperature, between 59° and 77°F (15-25°C). Store unused tablets in the original closed container.

How Supplied: CLOMICALM tablets are available in 5, 20, 40 and 80 mg tablet strengths in color-coded packaging for oral administration to dogs.

Keep this and all drugs out of reach of children.

Manufactured by: Virbac AH, Inc.
P.O. Box 162059, Fort Worth, TX 76161, USA

Approved by FDA under NADA # 141-120

04/24 - 03
302304

Virbac

PRODUCT INSERTS/DISCLOSURES

Cyclavance®

(cyclosporine oral solution) USP MODIFIED

100 mg/mL

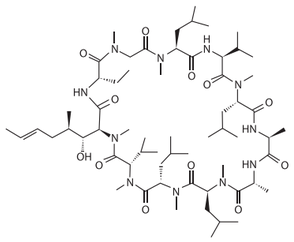
CAUTION: Federal (USA) Law restricts this drug to use by or on the order of a licensed veterinarian. Keep this and all drugs out of reach of children.

DESCRIPTION: CYCLAVANCE® (cyclosporine oral solution) USP MODIFIED is an oral form of cyclosporine that immediately forms a microemulsion in an aqueous environment. Cyclosporine, the active ingredient in CYCLAVANCE, is a cyclic polypeptide, immune modulating agent consisting of 11 amino acids. It is produced as a metabolite by the fungal species *Beauveria nivea.*

Chemically, cyclosporine A is designated Cyclo[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl].

INDICATIONS: CYCLAVANCE is indicated for the control of atopic dermatitis in dogs weighing at least 4 lbs (1.8 kg) body weight.

The structural formula is:



DOSAGE AND ADMINISTRATION: Always Provide the Instructions for Assembling the Dispensing System and Preparing a Dose of CYCLAVANCE and the Information for Dog Owners with the prescription. The initial dose of CYCLAVANCE is 5 mg/kg/day as a single daily dose for 30 days. Following this initial daily treatment period, the dose of CYCLAVANCE may be tapered by decreasing the frequency of dosing to every other day or twice weekly, until a minimum frequency is reached which will maintain the desired therapeutic effect. CYCLAVANCE should be given at least one hour before or two hours after a meal. If a dose is missed, the next dose should be administered (without doubling) as soon as possible but dosing should be no more frequent than once daily. The dispensing system for the 5 and 15 mL vial sizes includes a 1 mL oral dosing syringe graduated in 0.05 mL increments. To dose the dog, administer 0.05 mL of CYCLAVANCE per 2.2 lbs of body weight. The dispensing system for the 30 and 50 mL vial sizes includes both a 1 mL oral dosing syringe graduated in 0.05 mL increments, and a 3 mL oral dosing syringe graduated in 0.1 mL increments. To dose the dog, administer 0.1 mL of CYCLAVANCE per 4.4 lbs of body weight. **Do not rinse or clean the oral dosing syringe between uses.** (See **Instructions for Assembling the Dispensing System and Preparing a Dose of CYCLAVANCE**.)

CONTRAINDICATIONS: CYCLAVANCE is contraindicated for use in dogs with a history of neoplasia. Do not use in dogs with a hypersensitivity to cyclosporine.

WARNINGS: CYCLAVANCE (cyclosporine oral solution) is a systemic immunosuppressant that may increase the susceptibility to infection and the development of neoplasia.

HUMAN WARNINGS: Not for human use. Keep this and all drugs out of reach of children. **For use only in dogs. Special precautions to be taken when administering CYCLAVANCE in dogs:** Do not eat, drink, smoke, or use smokeless tobacco while handling CYCLAVANCE. Wear gloves during administration. **Wash hands after administration.** In case of accidental ingestion, seek medical advice immediately and provide the package insert or the label to the physician.
People with known hypersensitivity to cyclosporine should avoid contact with CYCLAVANCE.

PRECAUTIONS: The safety and effectiveness of cyclosporine has not been established in dogs less than 6 months of age or less than 4 lbs body weight. CYCLAVANCE is not for use in breeding dogs, pregnant or lactating bitches. As with any immunomodulation regimen, exacerbation of sub-clinical neoplastic and infectious conditions may occur. Gastrointestinal problems and gingival hyperplasia may occur at the initial recommended dose (See *Animal Safety*).

CYCLAVANCE may cause elevated levels of serum glucose, and should be used with caution in cases with diabetes mellitus. If signs of diabetes mellitus develop following the use of CYCLAVANCE, consideration should be given to tapering or discontinuing the dose.

CYCLAVANCE should be used with caution with drugs that affect the P-450 enzyme system. Simultaneous administration of CYCLAVANCE with drugs that suppress the P-450 enzyme system, such as azoles (e.g. ketoconazole), may lead to increased plasma levels of cyclosporine.

Since the effect of cyclosporine use on dogs with compromised renal function has not been studied, CYCLAVANCE should be used with caution in dogs with renal insufficiency.

There have been reports of convulsions in human adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone (See *Animal Safety*).

Killed vaccines are recommended for dogs receiving CYCLAVANCE because the impact of cyclosporine on the immune response to modified live vaccines is unknown (See *Animal Safety*).

ADVERSE REACTIONS: A total of 265 dogs were included in the field study safety analysis. One hundred and eleven (111) dogs were treated with placebo for the first 30 days. For the remainder of the study, all dogs received cyclosporine capsules.

Fourteen dogs withdrew from the study due to adverse reactions. Four dogs withdrew from the study after vomiting. One dog each withdrew from the study after diarrhea; vomiting, diarrhea and pruritus; vomiting, depression and lethargy; lethargy, anorexia and hepatitis; gingival hyperplasia, lethargy, polyuria/polydipsia and soft stool; seizure; sebaceous cyst; pruritus; erythema; or otitis externa.

Vomiting and diarrhea were the most common adverse reactions occurring during the study. In most cases, signs spontaneously resolved with continued dosing. In other cases, temporary dose modifications (brief interruption in dosing, divided dosing, or administration with a small amount of food) were employed to resolve signs.

Persistent otitis externa, urinary tract infections, anorexia, gingival hyperplasia, lymphadenopathy and lethargy were the next most frequent adverse events observed. Gingival hyperplasia regressed with dose tapering. Owners of four dogs reported seizures while dogs were receiving cyclosporine. In one dog, seizures were the result of a brain tumor diagnosed one month into the study. Another dog experienced seizures before and after the study.

Otitis externa, allergic otitis, or pinna erythema, with or without exudates, commonly accompanies atopy. Many dogs entered the study with otitis externa, which did not resolve without otic treatment. New cases of otitis externa, allergic otitis, or pinna erythema developed while dogs were receiving cyclosporine. However, the incidence rate was lower with cyclosporine compared to placebo. A change in the dose frequency was not necessary when new cases occurred.

Number of Dogs Displaying Each Clinical Observation in the Field Study

Clinical sign	% out of 265
Vomiting	30.9%
Diarrhea	20.0%
Persistent Otitis Externa	6.8%
Urinary Tract Infection	3.8%
Anorexia	3.0%
Lethargy	2.3%
Gingival Hyperplasia	2.3%
Lymphadenopathy	2.3%

The following clinical signs were reported in less than 2% of dogs treated with cyclosporine in the field study: constipation, flatulence, Clostridial organisms in the feces, nausea, regurgitation, polyuria/polydipsia, strong urine odor, proteinuria, pruritus, erythema/flushed appearance, pyoderma, sebaceous adenitis, crusty dermatitis, excessive shedding, coarse coat, alopecia, papillomas, histiocytoma, granulomatous mass or lesion, cutaneous cyst, epulis, benign epithelial tumor, multiple hemangioma, raised nodule on pinna, seizure, shaking/trembling, hind limb twitch, panting, depression, irritability, hyperactivity, quieter, increased light sensitivity, reluctance to go outside, weight loss, hepatitis.

The following clinical signs were observed in 1.5-4.5% of dogs while receiving the placebo: vomiting, diarrhea and urinary tract infection. The following clinical signs were observed in less than 1% of dogs receiving the placebo: anorexia, otitis externa, cutaneous cysts, corneal opacity, lymphadenopathy, erythema/flushed appearance.

Clinical Pathology Changes: During the study, some dogs experienced changes in clinical chemistry parameters while receiving cyclosporine, as described in the
following table:

Clinical Chemistry	% Affected (out of 265)
Elevated Creatinine	7.8%
Hyperglobulinemia	6.4%
Hyperphosphatemia	5.3%
Hyperproteinemia	3.4%
Hypercholesterolemia	2.6%
Hypoalbuminemia	2.3%
Hypocalcemia	2.3%
Elevated BUN	2.3%

In addition, the following changes in clinical chemistry parameters were noted in less than 2% of dogs: hypernatremia; hyperkalemia, elevated ALT, elevated ALP, hypercalcemia and hyperchloremia. These clinical pathology changes were generally not associated with clinical signs.

POST-APPROVAL EXPERIENCE: The following adverse events are based on post-approval adverse drug experience reporting. 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 grouped by body system and are presented in decreasing order of reporting frequency.

Gastrointestinal: Emesis, diarrhea, gingival hyperplasia, hemorrhagic diarrhea, abdominal pain, hematemesis, digestive tract hemorrhage, hypersalivation, retching, flatulence, tenesmus, intestinal stasis, digestive tract hypermotility, melena, pancreatitis, involuntary defecation

General: Lethargy, anorexia, weight loss, polydipsia, hyperthermia, pale mucous membrane, general pain, collapse, dehydration, edema

Dermatologic: Pruritus, dermatitis and eczema, alopecia, erythema, papilloma, bacterial skin infection, skin lesion, skin and/or appendage neoplasm, pigmentation disorder, hair change, hyperkeratosis, histiocytoma, fungal skin infection, dermal cyst(s), desquamation

Behavioral: Hyperactivity, behavioral changes, anxiety, vocalization, aggression, inappropriate urination, disorientation

Neurologic: Muscle tremor, convulsion, ataxia, paresis

Respiratory: Tachypnea, dyspnea, cough

Urologic: Polyuria, urine abnormalities (hematuria, urinary tract infection, proteinuria, glucosuria, decreased urine concentration) urinary incontinence, cystitis, renal failure, renal insufficiency

Immune: Urticaria, anaphylaxis, allergic edema

Blood and lymphatic: Lymphadenopathy, anemia, hypoalbuminemia, leukopenia

Hepatic: Elevated Liver Enzymes, hepatopathy, hepatomegaly, hepatitis

Musculoskeletal: Lameness, limb weakness, myositis

Ear and labyrinth: Otitis externa

Cardio-vascular: Tachycardia

Endocrine: Diabetes mellitus, hyperglycemia
In some cases, death/euthanasia has been reported as an outcome of the adverse events listed above.

Neoplasms have been reported in dogs taking cyclosporine, including reports of lymphoma/lymphosarcoma and mast cell tumor. It is unknown if these were preexisting or developed de novo while on cyclosporine.

Diabetes mellitus has been reported; West Highland White Terriers are the most frequently reported breed.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. 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: Cyclosporine is a immunosuppressive agent that has been shown to work via suppression of T-helper and T-suppressor cells and inhibition of interleukin-2. It does not depress hematopoiesis or the function of phagocytic cells. A decrease in CD4 and CD8 cells was not seen in dogs receiving 20 mg/kg/day of cyclosporine for 56 days. Cyclosporine is not a corticosteroid or an antihistamine.

METABOLISM: Cyclosporine is extensively metabolized by the cytochrome P-450 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents (See *Precautions*).

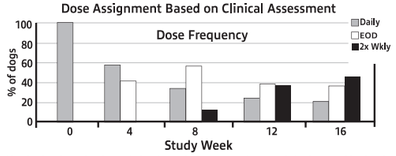
EFFECTIVENESS FIELD STUDY: A multisite, placebo controlled, double masked, field study was conducted in the United States and Canada using 16 investigators. Two hundred sixty five (265) dogs aged 1-10 years, weighing 4-121 lbs received either cyclosporine capsules at 5 mg/kg/day or placebo capsules. After 30 days, placebo dogs were switched to cyclosporine capsules.

Dogs were treated with cyclosporine capsules for a total of 4 months. No additional therapy with antihistamines, corticosteroids or medicated shampoos was permitted. Evaluations for pruritus and for skin lesions to derive a Canine Atopic Dermatitis Extent and Severity Index (CADESI) score occurred at enrollment and at monthly intervals. One hundred ninety-two (192) dogs were included in the statistical analysis of effectiveness.

At the end of the 30 day placebo controlled period, CADESI scores of dogs treated with cyclosporine capsules improved by 45% from enrollment, while CADESI scores of dogs treated with placebo worsened by 9%. Seventy-four percent (74%) of cyclosporine capsule treated dogs showed improvement in their pruritus scores over the first 30 day period, while only 24% of the placebo treated dogs showed an improvement. Owner and Veterinary Global Assessment in response to treatment also demonstrated statistically significant ($p<0.0001$) improvement. After 4 weeks of therapy, Owner and Veterinary Global Assessments showed approximately twice as much improvement in the cyclosporine capsule treated dogs as compared to placebo treated dogs.

Improvements in pruritus accompanied by 50% or 75% improvements in CADESI scores resulted in dose reductions to every other day or twice weekly respectively. Not all dogs were able to decrease to twice weekly dosing. Some animals required upward or downward dosage adjustments during the study. Such adjustments should be expected during therapy of this disease. Dogs unable to decrease from once daily dosing after 60 days were considered dose reduction failures for the purposes of the study.

The results of dose assignments, based on the study criteria, for each 4-week dosing period, are shown in the graph below.



Analysis of blood levels of cyclosporine drawn during the study demonstrated no correlation between blood cyclosporine levels and CADESI scores or pruritus; therefore monitoring blood cyclosporine levels is not an appropriate predictor of effectiveness.

ANIMAL SAFETY: In a 52-week oral study with dose levels of 0, 1, 3, and 9 times the target initial daily dose, emesis, diarrhea and weight loss were seen in all cyclosporine treated groups with increasing frequency as the dose increased.

Multilocular papilloma-like lesions of the skin were observed in 5 out of 8 high dose animals between weeks 20 and 40. These changes regressed spontaneously after drug was withdrawn.

Other findings in the mid and high dose animals included swollen gums due to chronic gingivitis and periodontitis, lower serum albumin and higher cholesterol, triglyceride, IgA and IgG. Hematological findings consisted of anemia and decreased leukocyte counts in a few high dose animals. Erythrocyte sedimentation rates were increased at all dose levels in a dose dependent fashion. Notable histopathological findings were limited to lymphoid atrophy, hypertrophic gums (from gingivitis) and slight regenerative changes of the renal tubular epithelium in high dose animals. The findings were shown to be reversible during a 12-week recovery phase of the study.

In a 90-day study with cyclosporine, dogs were dosed in one of two patterns: either 1, 3, or 5X the maximum recommended target initial daily dose for 90 days, or 1, 3, or 5X the maximum recommended target initial daily dose for 30 days followed by tapering to mimic the recommended clinical dosing pattern. The maximum recommended dose, when administered for 90 days causes callus-like lesions on the footpads, red/swollen pinnae, mild to moderate gingival proliferation, hyperkeratotic areas on the integument, hair loss, salivation, vomiting, and diarrhea/ abnormal stools. These clinical signs lessened in severity or resolved as the drug was tapered to a lower dose. Increased erythrocyte sedimentation rate, hyperproteinemia, hyperglobulinemia, hypoalbuminemia, hypocalcemia, hypophosphatemia, and hypomagnesemia were observed at three and five times the maximum recommended dose. These resolved as the dose was tapered.

When administered at higher than the maximum recommended dose, raised skin lesions, papilloma-like areas on the integument, popliteal lymph node enlargement, and weight loss were also seen. There were no cyclosporine related changes in urinalysis, ECG, blood pressure, or ophthalmologic exams.

Gross necropsy revealed epithelial changes consistent with those seen on physical examination. Proliferation of gingiva and toe pad epithelium was seen in all cyclosporine dosed groups, and was seen in a dose dependent fashion. The degree of the proliferation was greater in dogs in the non-tapered groups as compared to the tapered groups. Similar changes were noted on histopathologic examination of the cutaneous changes seen on physical examination. These lesions were characterized by epidermal hyperplasia, chronic dermatitis and hyperkeratosis.

Methylprednisolone combination: Twenty-four dogs were administered 1 mg/kg/day methylprednisolone alone for 14 days followed by 20 mg/kg/day cyclosporine either alone or in combination with methylprednisolone, or placebo for 14 days. There was no evidence of seizures/convulsions or neurological signs.

Vaccination effect: The effect of cyclosporine administration on the immunological response to vaccination was evaluated in a study in which 16 dogs were dosed with either cyclosporine at 20 mg/kg/day (4X the initial daily dose) or placebo for 56 days. All dogs were vaccinated on Day 27 with a killed commercial rabies virus and a multivalent vaccine (DHLPP) which included a modified live virus. Antibody titers for rabies, canine distemper, canine adenovirus type 2, parainfluenza, parvovirus, *Leptospira canicola,* and *Leptospira icterohaemmorrhagiae* were examined on Days 0, 27 (prior to vaccination), 42 and 56. Quantification of CD4, CD8, and CD3 T-lymphocytes was analyzed.

Clinical changes included soft stool and dermatologic changes consistent with those seen in previous studies. Antibody titers did not rise in dogs treated with cyclosporine or the placebo for any component of the multivalent vaccine which included a modified live virus while all animals demonstrated a significant increase in antibody rabies titer by Day 42 or 15 days post-revaccination. No effect was seen on T-lymphocytes.

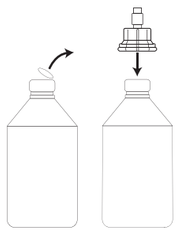
STORAGE INFORMATION: CYCLAVANCE® (cyclosporine oral solution) USP MODIFIED should be stored and dispensed in the original container at temperatures between 68-86°F (20-30°C).
Do not refrigerate because a precipitate may be observed below 68°F (20°C). **Once opened, use contents within 12 weeks.**

HOW SUPPLIED: CYCLAVANCE is supplied in glass amber vials of 5, 15, 30 and 50 mL at 100 mg/mL.
- 5 and 15 mL vials are supplied with a 1 mL Luer-Lok® oral dosing syringe.
- 30 and 50 mL vials are supplied with a 1 mL and 3 mL Luer-Lok® oral dosing syringes.

Instructions for Assembling the Dispensing System and Preparing a Dose of CYCLAVANCE® (cyclosporine oral solution) USP MODIFIED.

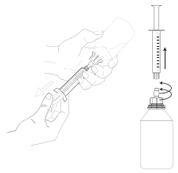
Assembling the Dispensing System

The dispensing system consists of three parts:
1. A vial containing the medicine sealed with a rubber stopper
2. A plastic adapter (dispensing system) that you will push onto the top of the vial. The adapter must always remain on the vial after first use.
3. An oral dosing syringe that fits into the top of the plastic adapter to withdraw the prescribed dose of medicine from the vial.
(1 mL syringe with the 5 and 15 mL vial sizes; 1 and 3 mL syringes with the 30 and 50 mL vial sizes)



Fitting the Plastic Adapter into the New Bottle of Medicine
1. Remove the plastic lid from the top of the vial.
2. Hold the vial upright on a table and align the stylet straight up and down over the center ring in the vial stopper. Push the plastic adapter firmly straight down onto the top of the vial until it is firmly and evenly seated.

Note: To prepare a dose, carefully follow the instructions for **Preparing a Dose of Medicine.**



Preparing a Dose of Medicine
1. Check that the plunger of the oral dosing syringe is pushed all the way down.
2. Keep the vial upright and push the oral dosing syringe firmly into the plastic adapter while turning the syringe clockwise to secure the dispensing system.
3. Turn the vial with the attached dosing syringe upside down and slowly pull the plunger down so that the oral dosing syringe fills with the medicine.
4. **Expel any large bubbles by pushing and pulling the plunger a few times. The presence of a few tiny bubbles is not important for dosing accuracy.**
5. Withdraw the dose of medicine prescribed by your veterinarian using the flange of the barrel to align with the marks on the plunger. These marks are in milliliters (mL).

Note: If the prescribed dose is more than the maximum volume marked on the oral dosing syringe, you will need to reload the syringe to withdraw the full dose.

6. Return the vial to its upright position and remove the oral dosing syringe by twisting it counterclockwise out of the plastic dispenser.

You can now introduce the syringe into the mouth of the dog according to your veterinarian's instructions, and push the medicine out of the syringe.

See **Information for Dog Owners** for complete administration instructions. To view an instructional video on Assembling the Dispensing System and Preparing a Dose of CYCLAVANCE, please go to https://vet-us.virbac.com/cyclavance

Do not rinse or clean the oral dosing syringe between uses.
Store the medication and the dosing syringe securely.
CYCLAVANCE should be stored and dispensed in the original container at temperatures between 68-86°F (20-30°C).
Do not refrigerate because a precipitate may be observed below 68°F (20°C).
Once opened, use contents within 12 weeks.

Keep out of reach of children

Approved by FDA under ANADA # 200-692

Manufactured for:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161
1-800-338-3659
us.virbac.com

02026053
Rev. 08/2022

easOtic®

(hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension for Dogs
Anti-inflammatory, antifungal, and antibacterial

Rx
For Otic Use in Dogs Only

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

DESCRIPTION
EASOTIC® Otic Suspension contains 1.11 mg/mL hydrocortisone aceponate, 17.4 mg/mL miconazole nitrate and 1.5 mg/mL gentamicin (as sulfate). The inactive ingredient is a semi-liquid petroleum jelly.

INDICATIONS
EASOTIC Otic Suspension is indicated for the treatment of otitis externa in dogs associated with susceptible strains of yeast *(Malassezia pachydermatis)* and bacteria *(Staphylococcus pseudintermedius)*.

DOSAGE AND ADMINISTRATION
Verify that the tympanic membrane is intact. **Shake well before each use.**

Priming the canister: Prior to the first use of the dosing container, press firmly on the pump several times, ensuring the pump goes all the way down, until the nozzle (cannula) fills with a full dose of product. Once the nozzle is filled with product it is ready for administration.

Carefully insert the cannula into the affected external ear canal(s) and apply 1 mL (a single pump) of EASOTIC Otic Suspension once per day for 5 days. Wash hands after usage.

CONTRAINDICATIONS
Do not use in dogs with known tympanic membrane perforation.

EASOTIC Otic Suspension is contraindicated in dogs with known or suspected hypersensitivity to corticosteroids, imidazole antifungals, or aminoglycoside antibiotics.

WARNINGS
Human Warnings: Not for use in humans. Keep this and all drugs out of reach of children. In case of accidental skin contact, wash area thoroughly with soap and water. Avoid contact with eyes.

Humans with known or suspected hypersensitivity to hydrocortisone, aminoglycoside antibiotics, or azole antifungals should not handle this product.

In case of accidental ingestion by humans, contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Animal Warnings: As a class, aminoglycoside antibiotics are associated with ototoxicity, vestibular dysfunction and renal toxicity. The use of EASOTIC Otic Suspension in a dog with a damaged tympanic membrane can result in damage to the structures of the ear associated with hearing and balance or in transmission of the infection to the middle or inner ear. Immediately discontinue use of EASOTIC Otic Suspension if hearing loss or signs of vestibular dysfunction are observed during treatment (see **ADVERSE REACTIONS**).

PRECAUTIONS
Do not administer orally.

Concurrent administration of potentially ototoxic drugs should be avoided.

Use with caution in dogs with impaired hepatic or renal function (see **ANIMAL SAFETY**).

Long-term use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs (see **ANIMAL SAFETY**).

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

ADVERSE REACTIONS
In a field study conducted in the United States (see **EFFECTIVENESS**), there were no adverse reactions reported in 145 dogs administered EASOTIC (hydrocortisone aceponate, miconazole nitrate, gentamicin sulfate) Otic Suspension for Dogs.

In foreign market experience, reports of hearing loss and application site erythema have been received. In most reported cases, the hearing loss and erythema were transient and resolved with discontinuation of EASOTIC Otic Suspension.

CONTACT INFORMATION
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

PHARMACOLOGY
Hydrocortisone aceponate is a glucocorticoid with anti-inflammatory effects. Miconazole nitrate is an imidazole antifungal. Gentamicin sulfate is an aminoglycoside antibiotic.

In the target animal safety study, hydrocortisone aceponate, miconazole and gentamicin were shown to be systemically absorbed from the ears of healthy dogs (see **ANIMAL SAFETY**); increased systemic absorption may be observed in inflamed ears.

MICROBIOLOGY
The compatibility and additive effect of each of the components in EASOTIC Otic Suspension was demonstrated in a component effectiveness and non-interference study. An in vitro study of organisms collected from clinical cases of otitis externa in dogs and from dogs enrolled in the clinical effectiveness study for EASOTIC Otic Suspension determined that miconazole nitrate and gentamicin sulfate inhibit the growth of bacteria and yeast commonly associated with otitis externa in dogs. No consistent synergistic or antagonistic effect of the two antimicrobials was demonstrated. The addition of hydrocortisone aceponate to the combination did not impair antimicrobial activity to any clinically-significant extent.

In a field study (see **EFFECTIVENESS**), the minimum of 10 isolates from successfully treated cases was met for *S. pseudintermedius* and *M. pachydermatis*.

EFFECTIVENESS
The effectiveness of this drug was evaluated in 157 dogs with otitis externa. The study was a double-masked field study with a placebo control. One hundred four dogs were treated with EASOTIC Otic Suspension and 53 dogs were treated with the placebo control. Treatment was administered once daily for 5 consecutive days to the affected ear(s). The dogs were evaluated at 4 different intervals over the course of 1 month to determine response to therapy. The 6 clinical signs evaluated were: malodor, aural discharge, pruritus, erythema, swelling and pain. The individual clinical scores were assigned based on the severity of each sign. Success was based on clinical improvement at Day 28 ± 2 days. The success rates of the 2 groups were significantly different (p=0.0179); 68.5% of dogs administered EASOTIC Otic Suspension were successfully treated, compared to 21.8% of the dogs in the placebo control group.

ANIMAL SAFETY
In the target animal safety study, EASOTIC Otic Suspension was administered at 0X, 1X, 3X and 5X the recommended dose for 15 consecutive days (3 times the recommended treatment duration) in laboratory Beagles, with 8 dogs per group. Hypersensitivity reactions in the external ear canal and inner pinnae were seen in all EASOTIC Otic Suspension groups and included mild to severe aural erythema (3X group), papules and ulceration (1X and 5X groups), otitis externa (3X and 5X groups), and otitis media (5X group). Renal tubular crystals were present in the cortex and medulla (0X, 1X, 3X, and 5X groups) and mild renal tubular basophilia and atrophy were present in one 5X group dog. Baseline cortisol values and the cortisol response to ACTH stimulation were lower in treated dogs compared to the control dogs. The ACTH stimulation test results are consistent with systemic absorption of topical corticosteroids causing suppression of the hypothalamic-pituitary-adrenal axis. Dogs in the 3X and 5X groups demonstrated elevations in AST and ALP, while dogs in the 1X, 3X, and 5X groups had elevated cholesterol, total protein, and albumin levels. Dogs in the 3X and 5X groups also had higher liver weights and greater food consumption.

STORAGE INFORMATION: Store at temperatures between 20°C-25°C (68°F-77°F), with excursions permitted between 15°C-30°C (59°F-86°F).

HOW SUPPLIED: EASOTIC Otic Suspension is supplied in a polyethylene canister, with a soft applicator cannula. Each canister contains ten 1 mL doses.

Made in the U.S.A.

Manufactured by:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161 USA

Approved by FDA under NADA # 141-330

Revision Date 04/2024

09420 302076-06

PRODUCT INSERTS/DISCLOSURES

Approved by FDA under ANADA # 200-071

0234
0302086-04

PRODUCT INFORMATION

EUTHASOL®
(pentobarbital sodium and phenytoin sodium) Euthanasia Solution

FOR DOGS ONLY

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

DESCRIPTION A non-sterile solution containing pentobarbital sodium and phenytoin sodium as the active ingredients. Rhodamine B, a bluish-red fluorescent dye, is included in the formulation to help distinguish it from parenteral drugs intended for therapeutic use. Although the solution is not sterile, benzyl alcohol, a bacteriostat, is included to retard the growth of microorganisms.

Each mL contains: Active ingredients: 390 mg pentobarbital sodium (barbituric acid derivative), 50 mg phenytoin sodium; *Inactive ingredients:* 10% ethyl alcohol, 18% propylene glycol, 0.003688 mg rhodamine B, 2% benzyl alcohol (preservative), water for injection q.s. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

ACTIONS EUTHASOL® Euthanasia Solution contains two active ingredients which are chemically compatible but pharmacologically different. Each ingredient acts in such a manner so as to cause humane, painless, and rapid euthanasia. Euthanasia is due to cerebral death in conjunction with respiratory arrest and circulatory collapse. Cerebral death occurs prior to cessation of cardiac activity.

When administered intravenously, pentobarbital sodium produces rapid anesthetic action. There is a smooth and rapid onset of unconsciousness. At the lethal dose, there is depression of vital medullary respiratory and vasomotor centers.

When administered intravenously, phenytoin sodium produces toxic signs of cardiovascular collapse and/or central nervous system depression. Hypotension occurs when the drug is administered rapidly.

Pharmacodynamic Activity The sequence of events leading to humane, painless, and rapid euthanasia following intravenous injection of EUTHASOL® Euthanasia Solution is similar to that following intravenous injection of pentobarbital sodium or other barbituric acid derivatives. Within seconds, unconsciousness is induced with simultaneous collapse of the dog. This stage rapidly progresses to deep anesthesia with concomitant reduction in the blood pressure. A few seconds later, breathing stops, due to depression of the medullary respiratory center; encephalographic activity becomes isoelectric, indicating cerebral death; and then cardiac activity ceases.

Phenytoin sodium exerts its effect during the deep anesthesia stage caused by the pentobarbital sodium. This ingredient, due to its cardiotoxic properties, hastens the stoppage of electrical activity in the heart.

INDICATIONS For use in dogs for humane, painless, and rapid euthanasia.

WARNING For canine euthanasia only. Must not be used for therapeutic purposes. Do not use in animals intended for food.

ENVIRONMENTAL HAZARD: This product is toxic to wildlife. Birds and mammals feeding on treated animals may be killed. Euthanized animals must be properly disposed of by deep burial, incineration, or other method in compliance with state and local laws, to prevent consumption of carcass material by scavenging wildlife.

HUMAN WARNING Caution should be exercised to avoid contact of the drug with open wounds or accidental self-inflicted injections. Keep out of reach of children. If eye contact, flush eyes with water and seek medical attention.

PRECAUTIONS Euthanasia may sometimes be delayed in dogs with severe cardiac or circulatory deficiencies. This may be explained by the impaired movement of the drug to its site of action. An occasional dog may elicit reflex responses manifested by motor movement; however, an unconscious animal does not experience pain, because the cerebral cortex is not functioning.

When restraint may cause the dog pain, injury, or anxiety, or danger to the person making the injection, prior use of tranquilizing or immobilizing drugs may be necessary.

DOSAGE AND ADMINISTRATION

Dosage: Dogs, 1 mL for each 10 pounds of body weight.

Administration: Intravenous injection is preferred. Intracardiac injection may be made when intravenous injection is impractical, as in a very small dog or in a comatose dog with impaired vascular functions. Good injection skill is necessary for intracardiac injection.

The calculated dose should be given in a single bolus injection.

For intravenous injection, a needle of sufficient gauge to ensure intravenous placement of the entire dose should be used.

The use of a Luer-Lok® syringe is recommended to prevent accidental exposure due to needle/syringe separation.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

HOW SUPPLIED EUTHASOL® Euthanasia Solution is available in 100 mL multiple dose vials.

STORAGE Store at controlled room temperature of between 20° and 25°C (68° and 77°F), with excursions permitted between 15° to 30°C (59° to 86°F).

Manufactured by a nonsterilizing process.

Manufactured for **Virbac AH, Inc.**, P.O. Box 162059, Fort Worth, TX 76161

GENESIS®
TOPICAL SPRAY
Solution of 0.015% triamcinolone acetonide

FOR TOPICAL USE IN DOGS ONLY

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

DESCRIPTION
GENESIS® Topical Spray contains 0.015% triamcinolone acetonide for dermatologic use. Each mL of GENESIS Topical Spray contains 0.15 mg triamcinolone acetonide in an aqueous solution containing propylene glycol, specially denatured alcohol, and DMDM hydantoin.

PHARMACOLOGY
Triamcinolone acetonide is highly potent synthetic glucocorticoid, which is primarily effective because of its anti-inflammatory activity. Topical corticosteroids can be absorbed from normal intact skin. Studies have demonstrated that topical preparations of triamcinolone have decreased plasma cortisol levels and suppressed the response to ACTH.

INDICATIONS
GENESIS Topical Spray is indicated for the control of pruritus associated with allergic dermatitis in dogs.

DOSAGE AND ADMINISTRATION
Apply sufficient pump sprays to uniformly and thoroughly wet the affected areas while avoiding run-off of excess product. Avoid getting the spray in dog's eyes. GENESIS Topical Spray should be administered twice daily for seven days, once daily for the next seven days, then every other day for an additional 14 days (28 days total).

DOSAGE AND ADMINISTRATION
Apply sufficient pump sprays to uniformly and thoroughly wet the affected areas while avoiding run-off of excess product. Avoid getting the spray in dog's eyes. GENESIS Topical Spray should be administered twice daily for seven days, once daily for the next seven days, then every other day for an additional 14 days (28 days total). To avoid overdosing the product, use the following table to determine the maximum number of pump sprays per treatment application. For mild pruritus or for small treatment surface areas, the number of pumps used should be less than this maximum amount.

Table 1. Maximum allowable dosage

Dog weight		Maximum number of pumps per single application*	Total maximum volume (mL) per 28 day treatment regimen
lb	kg		
11	5	4	101
22	10	7	176
33	15	11	277
44	20	15	378
55	25	19	478 (one 16-oz bottle)
66	30	22	554
77	35	26	655
88	40	30	756
99	45	33	832
110	50	37	932 (two 16-oz bottles)

*Using the recommended dosing regimen, there are two applications per day for the first week, one application per day for the second week and one application every other day for the last two weeks of treatment.

WARNINGS
User Safety: Wear gloves when applying the product. Spray in a well ventilated area. If the spray causes irritation to mucous membranes, discontinue use.

Keep this and all drugs out of reach of children.

Animal Safety: Clinical and experimental data have demonstrated that corticosteroids administered orally or by injection to animals may induce the first stage of parturition if used during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis. Additionally, corticosteroids administered to dogs, rabbits, and rodents during pregnancy have resulted in cleft palates in offspring. Corticosteroids administered to dogs during pregnancy have also resulted in other congenital anomalies including deformed forelegs, phocomelia, and anasarca.

PRECAUTIONS
The safety of this product for dogs less than eight pounds or for dogs less than one year of age has not been evaluated. The safety of this product in breeding, pregnant or lactating dogs has not been evaluated (see **WARNINGS**). The safety of long term or repeated use of this product (greater than 28 days) has not been evaluated.

Prolonged use or overdosage of any corticosteroid may produce adverse effects.

Because absorption of triamcinolone acetonide through topical application on the skin and by licking may occur, dogs receiving triamcinolone acetonide therapy should be observed closely for evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression. When the product was applied at approximately 6 times the maximum allowable dose (100 mL) once daily to normal skin of two dogs for five days, plasma cortisol levels were decreased after the first treatment and response to ACTH was reduced.

If adverse clinical signs are observed, treatment should be discontinued. Once the signs have disappeared, treatment can be resumed at a lower dose or frequency of application. If hypersensitivity to the product occurs, treatment should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

ADVERSE REACTIONS
In a field study with GENESIS Topical Spray, polyuria was reported in 3 of 57 dogs (5.3%) and polyphagia in 1 of 57 dogs (1.8%). Mild (within reference range) decreases in total leukocyte, lymphocyte and eosinophil counts were also reported. The following local reactions were reported in ≤ 3.6% of 110 dogs treated with GENESIS Topical Spray or the product vehicle: aversion/discomfort, sneezing and watery eyes.

EFFECTIVENESS
In a 28-day field study to demonstrate the effectiveness of GENESIS Topical Spray in controlling pruritus associated with allergic dermatitis in dogs under field conditions, 105 dogs with atopy, unspecified allergic dermatitis, flea allergy, and food allergy were treated with GENESIS Topical Spray at the recommended use level or placebo. Results are shown in Table 2.

Table 2. Percent of cases considered treatment successes

Treatment	Percent success[1]
GENESIS Topical Spray	35/54 = 64.8%*
Placebo	12/51 = 23.5%

[1]Success = reduction in the level of severity by two or more grades in the investigator's overall evaluation from the pre-treatment to the post-treatment evaluation period.
*Significantly different from placebo at $p < 0.05$

STORAGE CONDITIONS
Store at room temperature, 15° - 30° C (59° - 86° F).

HOW SUPPLIED
GENESIS Topical Spray is supplied in 8 ounce (237 mL) and 16 ounce (478 mL) bottles with spray applicators.

For technical information or to report adverse reactions, please call 1-800-338-3659.

Approved by FDA under NADA # 141-210.

Distributed by:
Virbac AH, Inc.
Fort Worth, TX 76161

Rev. 10/21

Virbac

PRODUCT INSERTS/DISCLOSURES

Virbac

1608247E
11605

Itrafungol®
(itraconazole oral solution)

10 mg/mL

Antifungal for oral use in cats only

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

Description
ITRAFUNGOL® (itraconazole oral solution) is a yellow to slightly amber, clear solution containing the active ingredient, itraconazole, at 10 mg/mL.

Indication
ITRAFUNGOL oral solution is indicated for the treatment of dermatophytosis caused by *Microsporum canis* in cats.

Dosage and Administration
The solution should be administered orally using the enclosed graduated dosing syringe.
The daily dosage is 5 mg/kg (0.5 mL/kg) body weight administered once daily on alternating weeks for 3 treatment cycles. Cats are treated during weeks 1, 3, and 5, and left untreated during weeks 2 and 4.

7 days	7 days	7 days	7 days	7 days
Daily treatment	No treatment	Daily treatment	No treatment	Daily treatment

Each line on the dosing syringe represents 0.05 mL of oral solution.

Table 1: Dose Table for ITRAFUNGOL oral solution

Weight of Cat	Volume of ITRAFUNGOL oral solution
0.5 lb	0.1 mL
1 lb	0.2 mL
1.5 lb	0.35 mL
2 lb	0.45 mL
2.5 lb	0.55 mL
3 lb	0.7 mL
3.5 lb	0.8 mL
4 lb	0.9 mL
4.5 lb	1 mL
5 lb	1.15 mL
6 lb	1.35 mL
7 lb	1.6 mL
8 lb	1.8 mL
9 lb	2 mL
10 lb	2.25 mL
11 lb	2.5 mL
12 lb	2.7 mL
13 lb	3 mL

The solution should be administered orally using the enclosed graduated dosing syringe. Keep the bottle upright and insert the dosing syringe through the opening of the top of the bottle (Figure 1). Do not invert the bottle (Figure 2). Fill the syringe by pulling the plunger until it reaches the graduation corresponding to the correct mL dose as indicated at the top of the syringe ring (Figure 3). Treat the cat by slowly and gently administering the liquid into the mouth, allowing the cat to swallow the product (Figure 4). For cats weighing more than 13.0 lbs, the total dose will need to be calculated and given over two doses as the dosing syringe only holds 3.0 mL of solution.

Fig 1

Fig 2

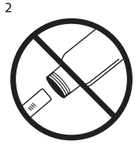


Fig 3

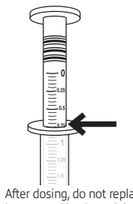


Fig 4

After dosing, do not replace syringe in the bottle. Rinse and dry the syringe. The bottle cap should be screwed back on tightly.

Contraindications
Do not administer to cats with hypersensitivity to itraconazole.

Warnings

User Safety Warnings
Not for use in humans. Keep this and all medications out of reach of children. Wash hands and exposed skin after use. In case of accidental contact with eyes, rinse thoroughly with water. In case of pain or irritation, seek medical advice. In case of accidental ingestion, rinse mouth with water and seek medical advice.
Special precautions for person administering the veterinary product to the animal:
Microsporum canis dermatophytosis is a zoonotic disease (a disease that can be transmitted from animals to humans); therefore consult a physician if a suspected lesion occurs on a human. Wear protective gloves when handling the animal during treatment or when cleaning the syringe. Wash hands and exposed skin after handling the animal.

ITRAFUNGOL (itraconazole oral solution) has not been shown to be sporicidal; therefore in order to reduce zoonotic potential, environmental contamination, and to decrease course of the disease, topical and environmental treatment should also be utilized.

Animal Safety Warnings
ITRAFUNGOL oral solution has not been shown to be safe in pregnant cats (see *Animal Safety*). ITRAFUNGOL oral solution should only be used in pregnant or lactating cats when the benefits outweigh the potential risks.

Keep ITRAFUNGOL oral solution in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions
ITRAFUNGOL oral solution has been associated with renal changes found on histopathology that were not noted after an eight week recovery period (see *Animal Safety*). Use with caution in cats with renal dysfunction.

ITRAFUNGOL oral solution is metabolized by the liver (mainly CYP3A) and can cause elevated liver enzymes (see *Animal Safety*). Use with caution in cats with impaired liver function and in cats currently being treated with other products that are metabolized by the liver. If clinical signs suggestive of liver disease develop, ITRAFUNGOL oral solution should be discontinued. Clinical signs of liver dysfunction requiring treatment have been observed in cats after ITRAFUNGOL oral solution use (see *Post-Approval Experience*).

ITRAFUNGOL oral solution is a cytochrome p-450 inhibitor and may increase or prolong plasma concentrations of other drugs metabolized by this pathway, such as amitriptyline, amlodipine, benzodiazepines, buspirone, cisapride, corticosteroids, cyclosporine, ivermectin, and macrolide antibiotics.

Negative inotropic effects have been reported in literature when itraconazole was administered intravenously to dogs and healthy human volunteers. Cats suffering from heart disease should be carefully monitored during treatment.

Adverse Reactions
In the laboratory effectiveness study, adverse reactions related to exposure to ITRAFUNGOL oral solution were primarily related to the gastrointestinal tract. Two ITRAFUNGOL-treated cats experienced transient hypersalivation during the dosing period. Vomiting was observed in 5 ITRAFUNGOL-treated cats (12.5%) during the dosing period compared to four cats (10%) in the control group. Diarrhea was observed in 9 ITRAFUNGOL-treated cats (22.5%) during the dosing period as compared to 7 cats (17.5%) in the control group.
One ITRAFUNGOL-treated cat showed mild increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at the end of the dosing period. No related clinical signs were observed, and these values returned to normal by the end of the follow-up period. One cat in the ITRAFUNGOL-treated group was noted to have lip erythema and lip induration once during the study. Field safety was evaluated in 266 cats randomized to receive itraconazole oral solution. Of the 266 cats that received at least one dose of itraconazole oral solution, adverse reactions included 35 cases (13%) of one or more elevated hepatic enzymes and 8 cases (3%) of gastrointestinal upset, including decreased appetite, vomiting and/or diarrhea. Other infrequent adverse reactions included less than 3 cases each of somnolence, depression, and increased salivation.

Post-Approval Experience (2021)
The following adverse events are based on post-approval adverse drug experience reporting for ITRAFUNGOL (itraconazole oral solution). 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 following adverse events reported in cats are listed in decreasing order of reporting frequency: Anorexia, emesis, elevated liver enzymes, lethargy, weight loss, icterus, elevated total bilirubin, and diarrhea.

Death (including euthanasia) has been reported. Some of these deaths were associated with the adverse events reported above.

(CONTINUED ON NEXT PAGE)

PRODUCT INSERTS/DISCLOSURES

(CONTINUED FROM PREVIOUS PAGE)

1608247E
11605

Contact Information
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. 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
The mode of action of itraconazole is based on its highly selective binding ability to fungal cytochrome p-450 iso-enzymes. This inhibits the synthesis of ergosterol and affects membrane-bound enzyme function and membrane permeability. This effect is irreversible and causes structural degeneration of the fungal organism.

Itraconazole was absorbed rapidly following oral administration of ITRAFUNGOL oral solution to laboratory cats. Compared to the fasted state, administration of ITRAFUNGOL oral solution with food results in slightly higher (1.3 fold) mean total itraconazole exposure (AUC), delay in median T_{max} (Fed 4 hours vs. Fasted 2 hours) and significant decrease (approximately 0.55 fold) in maximum plasma concentration (C_{max}). ITRAFUNGOL oral solution can be administered with or without food. Itraconazole oral solution binds extensively to plasma proteins (> 99%), and distributes well to tissues. More than 30 metabolites are formed. Hydroxy-itraconazole is the parent metabolite and has antifungal activity. Excretion is rapid and primarily via the feces.

In cats, a single oral dose of 5 mg/kg results in a C_{max} of 0.525 µg/mL post dose at 2 hours (T_{max}). The $AUC_{0\text{-}24h}$ is 5.09 µg·h/mL and the half-life in plasma is 12.1 hours. After repeated daily administration for seven days at 5 mg/kg/day, the C_{max} is doubled (1.05 µg/mL), the $AUC_{0\text{-}24h}$ is increased 3-fold (15.4 µg·h/mL) and the plasma half-life is increased to 36 hours.

In the therapeutic treatment schedule, itraconazole is almost completely cleared from plasma after each wash-out period. The hydroxy-itraconazole remains near or below the quantification limit in feline plasma after a single dose of itraconazole oral solution at 5 mg/kg. However, after repeated daily doses of itraconazole oral solution at 5 mg/kg for one week, the hydroxy-itraconazole C_{max} of 0.059 µg/mL was reached at 2 hours (T_{max}). Itraconazole concentrations in cat's hair vary; an increase occurs during treatment to a median value of 3.0 µg/g (mean 5.2 µg/g) at the end of the third dosing week and concentrations drop slowly to 1.5 µg/g (mean 1.9 µg/g) at 14 days after final dosing. Concentrations of hydroxy-itraconazole in hair are insignificant.

Effectiveness
Laboratory Study
Effectiveness was demonstrated using ITRAFUNGOL oral solution in a masked, placebo controlled laboratory study. Eighty cats were experimentally infected with *Microsporum canis* and treated with either ITRAFUNGOL oral solution or sterile water (control product) for the proposed therapeutic treatment schedule followed by a 4-week follow-up period. No topical therapy was used during this study. A statistical difference (P =0.0003) in mycological cure rate (defined as two consecutive negative mycological cultures) was demonstrated between cats treated with ITRAFUNGOL oral solution (24/40 or 60%) versus control (1/40 or 2.5%). Ninety percent of ITRAFUNGOL-treated cats (36/40) achieved at least one negative culture by the end of the study. Improvement was seen in inoculation site erythema and skin thickening by Day 7 and in crusts and scales by Day 14. By the end of the study, 98% of ITRAFUNGOL-treated cats had complete resolution of all clinical lesions, compared to 15% in the control group.
Wood's lamp cure (defined as no fluorescence at the base and mid-shaft of the hair) in the ITRAFUNGOL-treated group (39/40 or 97.5%) was higher compared to the control group (6/40 or 15%). Itraconazole MICs indicative of susceptibility were obtained in *M. canis* isolates from the two cats unsuccessfully treated with ITRAFUNGOL oral solution.

Field Study
A masked, positive-controlled, multi-site field study was conducted in client-owned cats in Europe. In this study, 514 cats diagnosed with dermatophytosis were randomly administered itraconazole oral solution or an active control. Cats received a daily dose of either itraconazole oral solution for three alternating weeks plus a placebo tablet once daily for 5 consecutive weeks, or a placebo solution for three alternating weeks plus the active control once daily for five weeks. Success was evaluated on clinical cure, which was noted with a complete resolution of all clinical lesions. Four weeks after the end of treatment, 175 (83%) out of 207 cats treated with itraconazole oral solution were clinically cured.

Animal Safety
Margin of Safety Study with Recovery
In a margin of safety study, ITRAFUNGOL (itraconazole oral solution) was administered orally to 9-10 week old healthy kittens once daily at 0X (saline control), 1X (5 mg/kg), 3X (15 mg/kg), and 5X (25 mg/kg) the therapeutic dose for 17 alternating weeks (9 total weeks of dosing) followed by an 8 week recovery period. Hypersalivation during or immediately following dosing, vomiting, and loose stool were the most frequent abnormal clinical observations related to treatment with ITRAFUNGOL oral solution. Hypersalivation was limited to the 3X and 5X groups and was observed in every dosing cycle. Vomiting was noted at similar levels in the control, 1X and 3X groups; however, it occurred approximately twice as often in the 5X group. Mild gingival bleeding and perioral irritation (patchy alopecia and erythema) was noted in cats in the 3X and 5X groups. Food consumption was consistently higher throughout the study in the control group than the ITRAFUNGOL oral solution groups. The control group gained more weight during the study than the groups administered ITRAFUNGOL oral solution. Mild elevations in ALT were sporadically noted in all groups; however, the number of affected cats increased with the higher doses (two cats in the control group, two cats in the 1X group, three cats in the 3X group, and four cats in the 5X group). In most cats, ALT values peaked just above the upper limit of the reference range and were continuing to trend upward or were elevated yet stable at the end of the study. One cat in the 5X group exhibited inappetence progressing to anorexia, dehydration and vomiting during the first dosing cycle. This cat had repeated episodes of inappetence during the second and third dosing cycles. This cat also had markedly elevated ALT and AST values on Day 36 (693 U/L and 283 U/L, respectively), was treated with minimal supportive care and recovered to complete the study.

Margin of Safety Study
In a margin of safety study, ITRAFUNGOL oral solution was administered orally to healthy adult cats once daily at 0X (saline control), 1X (5 mg/kg), 3X (15 mg/kg), and 5X (25 mg/kg) the therapeutic dose for 17 alternating weeks (9 total weeks of dosing) with no recovery period. Hypersalivation was the most frequent abnormal clinical observation related to treatment with ITRAFUNGOL oral solution and the incidence increased with the higher doses. One cat in group 4 (5X; Cat #26302) lost 22% of its body weight and had a number of episodes of vomiting, salivation, and anorexia during the treatment period. This cat also had renal lesions found on histopathology. Increasing trends were noted in ALT, AST, and creatinine values in some cats administered ITRAFUNGOL oral solution as compared to baseline values. Abnormal renal findings included proximal convoluted tubule acute degeneration in 3 cats in the 1X group and 3 cats in the 5X group; one 5X cat (cat #26302) also had proximal convoluted tubule marked pallor and focal mononuclear cell infiltration in the kidneys. In the lungs, one 3X group cat and five 5X cats had intra-alveolar foamy macrophages; five 5X group cats had intra-alveolar syncytial cells.

These histopathology findings are likely related to exposure to ITRAFUNGOL oral solution, specifically the vehicle component hydroxypropyl-ß-cyclodextrin (HPßCD). There were no corresponding adverse clinical effects noted on observation or on clinical pathology analysis. In addition, similar changes have been described in literature in other species exposed to HPßCD and have been reported to be reversible.

Reproductive Safety
In a study of 16 pregnant queens administered itraconazole oral solution at 5 mg/kg bodyweight for a total of 21 days (7 days on alternate weeks) during gestation or lactation, there was a high frequency of fetal resorption (partial and total), abnormal fetuses, and abnormal maternal behaviors. Confounding factors, such as infectious disease *(Chlamydia psittaci)* in some cats made it difficult to establish a definitive relationship between administration of itraconazole and the abnormal findings. However, the results of this study reveal potential reproductive safety risks and do not support the safe use of ITRAFUNGOL oral solution in pregnant queens.

Storage conditions
Store at 68-77°F (20-25°C). Excursions permitted between 59-86°F (15-30°C).

How supplied
ITRAFUNGOL oral solution is available in a glass bottle containing 52 mL of oral solution, closed with a child resistant screw cap and packaged in a cardboard box that includes a package insert and a graduated dosing syringe.

Approved by FDA under NADA # 141-474

Manufactured for Virbac AH, Inc., P.O. Box 162059, Fort Worth, TX 76161

Version Date: February 2023
1608247E

IVERHART MAX® Chew
(ivermectin/pyrantel pamoate/praziquantel)

For oral use in dogs only.

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: IVERHART MAX® Chew is a combination of three anthelmintics (ivermectin/pyrantel pamoate/praziquantel). The chews are available in four sizes in color-coded packages for oral administration to dogs according to their weight **(see Dosage and Administration)**.

Indications: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of roundworms (*Toxocara canis, Toxascaris leonina*), hookworms (*Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense*), and tapeworms (*Dipylidium caninum, Taenia pisiformis*).

Dosage and Administration: IVERHART MAX Chew should be administered orally at monthly intervals and the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb), 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) and 5 mg of praziquantel per kg (2.27 mg/lb) of body weight, as follows:

Dog Weight Pounds	Chew per Month	Chew Size	Ivermectin Content	Pyrantel Pamoate Content	Praziquantel Content
6.0 to 12	1	Toy	34 mcg	28.5 mg	28.5 mg
12.1 to 25	1	Small	68 mcg	57 mg	57 mg
25.1 to 50	1	Medium	136 mcg	114 mg	114 mg
50.1 to 100	1	Large	272 mcg	228 mg	228 mg

IVERHART MAX Chew is recommended for dogs 8 weeks of age or older. For dogs over 100 lbs, use the appropriate combination of these soft chews.

Remove only one dose at a time from the packaging. Return the remaining chew(s) to their box to protect from light. The chew can be offered to the dog by hand or added, intact, to a small amount of dog food. Care should be taken to ensure that the dog consumes the complete dose. The treated dog should be observed for a few minutes after administration to confirm that none of the dose has been lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

IVERHART MAX Chew should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventative product in a heartworm disease prevention program, the first dose of IVERHART MAX Chew must be given within a month (30 days) after the last dose of the former medication. A heartworm test should be performed prior to and 6 months after switching heartworm preventative products.

If the interval between doses exceeds a month (30 days), the effectiveness of ivermectin can be reduced. Therefore, for optimal performance, the chew must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with IVERHART MAX Chew and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Warnings:
For use in dogs only. Keep this and all drugs out of reach of children and pets. In safety studies with ivermectin/pyrantel pamoate/praziquantel tablets, testicular hypoplasia was observed in some dogs receiving 3 and 5 times the maximum recommended dose monthly for 6 months (see Animal Safety).

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Precautions: Use with caution in sick, debilitated, or underweight animals and dogs weighing less than 10 lbs (see Animal Safety). The safe use of this drug has not been evaluated in pregnant or lactating bitches.

All dogs should be tested for existing heartworm infection before and 6 months after starting treatment with IVERHART MAX Chew, which is not effective against adult *Dirofilaria immitis*. Infected dogs should be treated to remove adult heartworms and microfilariae before initiating a heartworm prevention program.

While some microfilariae may be killed by the ivermectin in IVERHART MAX® Chew at the recommended dose level, IVERHART MAX Chew is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Adverse Reactions: In a field study with IVERHART MAX Chew, self-limiting adverse reactions, including vomiting, diarrhea, lethargy, difficulty swallowing, excessive salivation, increased water consumption, and coughing were reported. Self-limiting adverse reactions, including lethargy, limpness, salivation, shaking, diarrhea, decreased appetite, licking lips, and belching were reported between 20 minutes and 72 hours following treatment in a field study with ivermectin/pyrantel pamoate/praziquantel tablets.

In field studies with ivermectin/pyrantel/praziquantel pamoate tablets, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported in dogs following the use of ivermectin products: depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions, and hypersalivation.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

Effectiveness: Prevention of the tissue larval stage of heartworm (*Dirofilaria immitis*) and the elimination of the adult stage of hookworm (*Ancylostoma caninum, Uncinaria stenocephala, Anyclostoma braziliense*), roundworm (*Toxocara canis, Toxascaris leonina*), and tapeworm (*Dipylidium caninum, Taenia pisiformis*) infections in dogs was demonstrated in well-controlled laboratory studies.

Palatability: In a field study of 132 dogs, IVERHART MAX Chew was offered once monthly for 3 months. The dogs voluntarily consumed 86.3% of the doses from the owner's hand or from a bowl within 5 minutes, 13.0% accepted the dose when it was offered in food or administered by placing in the back of the dog's tongue (pilling), and 0.7% of the doses were unable to be administered.

Animal Safety: Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target dose level of 6 mcg/kg) than dogs of other breeds. At elevated doses, sensitive dogs showed more adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. No signs of toxicity were seen at 10 times the recommended dose (27.2 mcg/lb) in sensitive Collies. Data from these studies support the safety of ivermectin products in dogs, including Collies, when used at the label recommended dose.

Because ivermectin and praziquantel are approximately 30% more bioavailable in the IVERHART MAX Chew than in the ivermectin/pyrantel pamoate/praziquantel tablets used in the following target animal safety studies, the margin of safety is narrower than reported in these studies. The potential for adverse reactions may be greater in individual dogs administered IVERHART MAX Chew than ivermectin/pyrantel pamoate/praziquantel tablets.

In a target animal safety study using ivermectin/pyrantel pamoate/praziquantel tablets, doses were administered to 8 week old Beagle puppies at one, three, and five times the maximum recommended dose of 12.5 mcg/kg ivermectin, 10.47 mg/kg pyrantel and 10.47 mg/kg praziquantel. The dogs were treated every 30 days for 6 months. Vomiting within 6 hours of dosing and soft or watery feces within 24 hours of dosing were observed. Other observations during the study were: ano-genital swelling, lethargy, head movements, shallow, audible or difficult breathing, and salivation. One dog in the 5X group had tremors and decreased activity. All of these signs were transient. No treatment was required. Histopathology showed testicular hypoplasia in the 3X and 5X groups **(see Warnings)**.

In a laboratory safety study using ivermectin/pyrantel pamoate/praziquantel tablets, 12-week-old Beagle puppies receiving 3 and 5 times the recommended dose once weekly for 13 weeks demonstrated a dose-related decrease in testicular maturation compared to controls. In this study, all treated puppies had significantly higher cholesterol levels compared to untreated controls.

In a reproductive safety study, adult males were treated at 37.5 mcg/kg ivermectin, 31.4 mg/kg pyrantel and 31.4 mg/kg praziquantel every 14 days during two full spermatogenic cycles (112 days). The quality of semen and reproductive health were not affected by treatment. Treatment related vomiting and soft feces were reported during this study.

In a study of the effectiveness of ivermectin/pyrantel pamoate/praziquantel tablets for the treatment of *Toxocara canis*, one 8.1 lb, 72-day-old puppy died 6 days after administration of the label dose. This puppy and many other puppies in the study had high worm burdens and were reported to have diarrhea, sometimes bloody, frequently before and after treatment. Dehydration and signs of anemia (pale mucous membranes) were the only abnormal gross necropsy finding observed. No definitive cause was determined. In a 90-day field study using ivermectin/pyrantel pamoate/praziquantel tablets, the most serious adverse reactions (lethargy, limpness, and salivation) were seen in dogs weighing less than 10 lbs **(see Precautions)**.

Storage Information: Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F to 86°F). Protect product from light.

How Supplied: IVERHART MAX Chew is available in four dosage strengths **(see Dosage and Administration)** for dogs of different weights. Each strength comes in a package of 6 chews.

Approved by FDA under NADA # 141-441

Manufactured by:

Virbac AH, Inc.
Fort Worth, TX 76137 USA
Phone: 1-800-338-3659

302143-04
10/2020

Virbac Shaping the future of animal health

IVERHART PLUS®
(ivermectin/pyrantel)
Flavored Chewables

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

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae *(Dirofilaria immitis)* for a month (30 days) after infection and for the treatment and control of roundworms *(Toxocara canis, Toxascaris leonina)* and hookworms *(Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense)*.

DOSAGE: *IVERHART* PLUS® (ivermectin/pyrantel) *Flavored Chewables* should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of roundworms and hookworms is as follows:

Dog Weight	Flavored Chewable Per Month	Ivermectin Content	Pyrantel Content
Up to 25 lbs	1	68 mcg	57 mg
26 to 50 lbs	1	136 mcg	114 mg
51 to 100 lbs	1	272 mcg	227 mg

IVERHART PLUS *Flavored Chewables* are recommended for dogs 6 weeks of age and older. For dogs over 100 lbs use the appropriate combination of these flavored chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find *IVERHART* PLUS *Flavored Chewables* palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food. The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

IVERHART PLUS *Flavored Chewables* should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of *IVERHART* PLUS *Flavored Chewables* must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the flavored chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with *IVERHART* PLUS *Flavored Chewables* and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with *IVERHART* PLUS *Flavored Chewables* also provides effective treatment and control of roundworms (*T. canis, T. leonina*) and hookworms (*A. caninum, U. stenocephala, A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: *IVERHART* PLUS *Flavored Chewables*, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D. immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. *IVERHART* PLUS *Flavored Chewables* are also effective against canine roundworms (*T. canis, T. leonina*) and hookworms (*A. caninum, U. stenocephala, A. braziliense*).

ACCEPTABILITY: In a trial in client-owned dogs, *IVERHART* PLUS *Flavored Chewables* were shown to be a palatable oral dosage form consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with *IVERHART* PLUS *Flavored Chewables*, which are not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with *IVERHART* PLUS *Flavored Chewables.*

While some microfilariae may be killed by the ivermectin in *IVERHART* PLUS *Flavored Chewables* at the recommended dose level, *IVERHART* PLUS *Flavored Chewables* are not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

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

Warnings: Use product on or before its expiration date.
Discard or return unused tablets.

ADVERSE REACTIONS: In clinical trials with ivermectin/pyrantel, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of ivermectin: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

SAFETY: Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level of 6 mcg/kg) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. Ivermectin demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of ivermectin products in dogs, including Collies, when used as recommended.

Ivermectin/pyrantel has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with ivermectin/pyrantel in a heartworm disease preventive program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: *IVERHART* PLUS *Flavored Chewables* are available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in a box of 6 tablets, packed 10 boxes per display box.

Approved by FDA under ANADA # 200-302

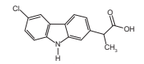
Manufactured by: Virbac AH, Inc.
Fort Worth, TX 76161, USA
301732-07
03/23

PRODUCT INSERTS/DISCLOSURES

MOVODYL™ Chewable Tablets
(carprofen)
Non-steroidal anti-inflammatory drug
For oral use in dogs only

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

DESCRIPTION:
MOVODYL Chewable Tablets (carprofen) are a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen,and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273.72. The chemical structure of carprofen is:



Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

CLINICAL PHARMACOLOGY:
Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models[1].

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals[2]. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species[3]. In an *in vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4] Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions[1].

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses[5,6]. Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, , and PGE_2 by its inhibitory effect in prostaglandin biosynthesis[7].

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally[10]. Peak blood plasma concentrations are achieved in 1-3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5-9.8 hours) after single oral doses varying from 1-35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Carprofen is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70-80%) and urine (10-20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS:
MOVODYL Chewable Tablets are indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS:
MOVODYL Chewable Tablets should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS:
Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only**. Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners, Adverse Reactions, Animal Safety and Post-Approval Experience).**

PRECAUTIONS:
As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid[11,16]. When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients[12,14]. NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy[11,14]. The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of MOVODYL Chewable Tablets (carprofen) with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Carprofen treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to ten times the dose in healthy dogs.

MOVODYL Chewable Tablets are not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of MOVODYL Chewable Tablets in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Studies to determine the activity of MOVODYL Chewable Tablets when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed[15].

If additional pain medication is warranted after administration of the total daily dose of MOVODYL Chewable Tablets, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroids use to NSAID use.

Due to the flavoring contained in MOVODYL Chewable Tablets, store out of the reach of dogs and in a secured area. Severe adverse reactions may occur if large quantities of tablets are ingested. If you suspect your dog has consumed MOVODYL Chewable Tablets above the labeled dose, please call your veterinarian for immediate assistance and notify Virbac AH, Inc. (1-800-338-3659).

INFORMATION FOR DOG OWNERS:
MOVODYL Chewable Tablets, like other drugs of its class, are 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 decreased appetite, vomiting, diarrhea, 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 MOVODYL Chewable Tablets therapy 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.

ADVERSE REACTIONS:
During investigational studies for the caplet formulation with twice daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen caplet- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control.

There were no serious adverse events reported during clinical field studies with once daily administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2mg/lb once daily)

Observation	Carprofen (n=129)	Placebo (n=132)
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	-
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; medical judgment is necessary to determine clinical relevance.

During investigational studies of surgical pain for the caplet formulation, no clinically significant adverse reactions were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Surgical Pain Field Studies with Caplets (2 mg/lb once daily)

Observation*	Carprofen (n=148)	Placebo (n=149)
Vomiting	10.1	13.4
Diarrhea/soft stool	6.1	6.0
Ocular disease	2.7	0
Inappetence	1.4	0
Dermatitis/Skin lesion	2.0	1.3
Dysrhythmia	0.7	0
Apnea	1.4	0
Oral/Periodontal disease	1.4	0
Pyrexia	0.7	1.3
Urinary tract disease	1.4	1.3
Wound drainage	1.4	0

*A single dog may have experienced more than one occurrence of an event

During investigational studies for the chewable tablet formulation, gastrointestinal signs were observed in some dogs. These signs included vomiting and soft stools.

Post-Approval Experience:
Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions listed above.

Contact Information
Contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. To report suspected adverse drug experiences, contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

DOSAGE AND ADMINISTRATION:
Always provide Client Information Sheet with prescription. Carefully consider the potential benefits and risk of MOVODYL Chewable Tablets (carprofen) and other treatment options before deciding to use MOVODYL Chewable Tablets. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for oral administration to dogs is 2 mg/lb of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. MOVODYL Chewable Tablets are scored and dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. MOVODYL Chewable Tablets may be fed by hand or placed in food. Care should be taken to ensure that the dog consumes the complete dose. Half-tablets should be used within 90 days.

EFFECTIVENESS:
Confirmation of the effectiveness of carprofen for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries, was demonstrated in 5 placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of carprofen caplets in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of carprofen caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily.

In these 2 field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered carprofen caplets at labeled doses.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of carprofen caplets for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered carprofen preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered carprofen showed statistically significant reduction in pain scores compared to controls.

ANIMAL SAFETY:
Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that carprofen is well tolerated in dogs after oral administration.

In target animal safety studies, carprofen was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dl after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52-week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for carprofen-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in carprofen). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. In the latter study, 3 carprofen-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with laboratory value changes. Changes in clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant. The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted in 297 dogs of different breeds undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of carprofen two hours prior to surgery then once daily, as needed for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Carprofen was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observation in carprofen- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in carprofen- and placebo-treated animals. Changes in clinicopathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 7.3 IU and 2.5 IU less than pre-treatment values for dogs receiving carprofen and placebo, respectively. The mean post-treatment AST values were 3.1 IU less for dogs receiving carprofen and 0.2 IU greater for dogs receiving placebo.

STORAGE:
Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). [See USP controlled room temperature.] Protect from light.

HOW SUPPLIED:
MOVODYL Chewable Tablets (carprofen) are scored (except for the unscored 37.5 mg strength), and contain 25 mg, 50 mg, 37.5 mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 60 or 180 tablets.

REFERENCES:
1. Baruth H, *et al*: In Anti-Inflammatory and Anti-Rheumatic Drugs, Vol. II, Newer Anti-Inflammatory Drugs, Rainsford KD, ed. CRC Press, Boca Raton, p. 33, 1986.
2. Vane JR, Botting RM: Mechanism of action of anti-inflammatory drugs. *Scand J Rheumatol* 25:102, pp. 9–21.
3. Grossman CJ, Wiseman J, Lucas FS, *et al*: Inhibition of constitutive and inducible cyclooxygenase activity in human platelets and mononuclear cells by NSAIDs and Cox-2 inhibitors. *Inflammation Research* 44:253–257, 1995.
4. Ricketts AP, Lundy KM, Seibel SB: Evaluation of selective inhibition of canine cyclooxygenase 1 and 2 by carprofen and other nonsteroidal anti-inflammatory drugs. *Am J Vet Res* 59:11, pp. 1441–1446, November 1998.
5. Ceuppens JL, *et al*: Non-steroidal anti-inflammatory agents inhibit the synthesis of IgM rheumatoid factor *in vitro*. *Lancet* 1:528, 1982.
6. Ceuppens JL, *et al*: Endogenous prostaglandin E, enhances polyclonal immunoglobulin production by ionically inhibiting T suppressor cell activity. *Cell Immunol* 70:41, 1982.
7. Schleimer RP, *et al*: The effects of prostaglandin synthesis inhibition on the immune response. *Immunopharmacology* 3:205, 1981.
8. Leung KH, *et al*: Modulation of the development of cell mediated immunity: Possible roles of the products of cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. *Int J Immunopharmacology* 4:195, 1982.
9. Veit BC: Immunoregulatory activity of cultured-induced suppressor macrophages. *Cell Immunol* 72:14, 1982.
10. Schmitt M, *et al*: Biopharmaceutical evaluation of carprofen following single intravenous, oral, and rectal doses in dogs. *Biopharm Drug Dispos* 11(7):585, 1990.
11. Kore AM: Toxicology of nonsteroidal anti-inflammatory drugs Veterinary Clinics of North America, *Small Animal Practice* 20, March 1990.
12. Binns SH: Pathogenesis and pathophysiology of ischemic injury in cases of acute renal failure. *Compend for Cont Ed* 16:1, January 1994.
13. Boothe DM: Prostaglandins: Physiology and clinical implications. *Compend for Cont Ed* 6:11, November 1984.
14. Rubin SI: Nonsteroidal anti-inflammatory drugs, prostaglandins, and the kidney. *JAVMA* 188:9, May 1986.
15. Ko CH, Lange DN, Mandsager RE, *et al*: Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs. *JAVMA* 217:1025–1028, 2000.

Approved by FDA under ANADA # 200-687

Manufactured for:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161
1-800-338-3659

4206162/TS/DRUGS/2023
Made in India
PC00960- 00
Rev: No: 02

TAKE TIME OBSERVE LABEL DIRECTIONS

Issued: June 2024

PRODUCT INSERTS/DISCLOSURES

PARASEDGE™ Multi for Dogs (imidacloprid + moxidectin) Topical Solution

Once-a-month topical solution for the prevention of heartworm disease, the treatment of circulating microfilariae, kills adult fleas, is indicated for the treatment of flea infestations, the treatment and control of sarcoptic mange, as well as the treatment and control of intestinal parasite infections in dogs and puppies that are at least 7 weeks of age and that weigh at least 3 lbs.

WARNING
- **DO NOT ADMINISTER THIS PRODUCT ORALLY**
- **For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals.**
- **Children should not come in contact with application sites for two (2) hours after application (See Contraindications, Warnings, Human Warnings, and Adverse Reactions, for more information.)**

CAUTION:
Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
PARASEDGE™ Multi for Dogs (10 % imidacloprid + 2.5 % moxidectin) is a colorless to yellow ready-to-use solution packaged in single dose applicator tubes for topical treatment of dogs. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin based on body weight.

Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name for imidacloprid is 1-[(6-Chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine. Moxidectin is a semisynthetic macrocyclic lactone endectocide derived from the actinomycete *Streptomyces cyaneogriseus noncyanogenus*. The chemical name for moxidectin is [6R, 23E, 25S(E)]-5-O-Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

INDICATIONS:
PARASEDGE™ Multi for Dogs is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs. PARASEDGE™ Multi for Dogs kills adult fleas and is indicated for the treatment of flea infestations (*Ctenocephalides felis*). PARASEDGE™ Multi for Dogs is indicated for the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei var. canis*. PARASEDGE™ Multi for Dogs is also indicated for the treatment and control of the following intestinal parasites:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma caninum*	X	X	X
	Uncinaria stenocephala	X	X	X
Roundworm Species	*Toxocara canis*	X		X
	Toxascaris leonina	X		
Whipworm	*Trichuris vulpis*	X		

CONTRAINDICATIONS:
Do not administer this product orally. (See WARNINGS.)
Do not use this product (containing 2.5 % moxidectin) on cats.

WARNINGS:
For the first 30 minutes after application:
Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs.

Separate treated dogs from one another and from other pets to reduce the risk of accidental ingestion.

Ingestion of this product by dogs may cause serious adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors.

In avermectin sensitive dogs,[a] the signs may be more severe and may include coma and death.[b]

[a] Some dogs are more sensitive to avermectins due to a mutation in the MDR1 gene. Dogs with this mutation may develop signs of severe avermectin toxicity if they ingest this product. The most common breeds associated with this mutation include Collies and Collie crosses.

[b] Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children.
Children should not come in contact with application sites for two (2) hours after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headache; dizziness; and redness, burning, tingling, or numbness of the skin. **Wash hands thoroughly with soap and warm water after handling.**

If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice.

The safety data sheet (SDS) provides additional occupational safety information. To report suspected adverse drug events, for technical assistance or to obtain a copy of the SDS, contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.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:
Do not dispense dose applicator tubes without complete safety and administration information.

Use with caution in sick, debilitated, or underweight animals. The safety of PARASEDGE™ Multi for Dogs has not been established in breeding, pregnant, or lactating dogs. The safe use of PARASEDGE™ Multi for Dogs has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight.

Prior to administration of PARASEDGE™ Multi for Dogs, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of PARASEDGE™ Multi for Dogs has not been evaluated when administered on the same day as an adulticide. PARASEDGE™ Multi for Dogs is not effective against adult *D. immitis*. Although the number of circulating microfilariae is substantially reduced in most dogs following treatment with PARASEDGE™ Multi for Dogs, the microfilaria count in some heartworm-positive dogs may increase or remain unchanged following treatment with PARASEDGE™ Multi for Dogs alone or in a dosing regimen with melarsomine dihydrochloride. **(See ADVERSE REACTIONS and ANIMAL SAFETY - Safety Study in Heartworm-Positive Dogs.)**

PARASEDGE™ Multi for Dogs has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

ADVERSE REACTIONS:

Heartworm-Negative Dogs

Field Studies: Following treatment with imidacloprid and moxidectin topical solution or an active control, dog owners reported the following post-treatment reactions:

OBSERVATION	imidacloprid and moxidectin topical solution n=128	Active Control n=68
Pruritus	19 dogs (14.8 %)	7 dogs (10.3 %)
Residue	9 dogs (7.0 %)	5 dogs (7.4 %)
Medicinal Odor	5 dogs (3.9 %)	None observed
Lethargy	1 dog (0.8 %)	1 dog (1.5 %)
Inappetence	1 dog (0.8 %)	1 dog (1.5 %)
Hyperactivity	1 dog (0.8 %)	None observed

During a field study using 61 dogs with pre-existing flea allergy dermatitis, one (1.6 %) dog experienced localized pruritus immediately after imidacloprid application, and one investigator noted hyperkeratosis at the application site of one dog (1.6 %).

In a field safety and effectiveness study, imidacloprid and moxidectin topical solution was administered to 92 client-owned dogs with sarcoptic mange. The dogs ranged in age from 2 months to 12.5 years and ranged in weight from 3 to 231.5 pounds. Adverse reactions in dogs treated with imidacloprid and moxidectin topical solution included hematochezia, diarrhea, vomiting, lethargy, inappetence, and pyoderma.

Laboratory Effectiveness Studies: One dog in a laboratory effectiveness study experienced weakness, depression, and unsteadiness between 6 and 9 days after application with imidacloprid and moxidectin topical solution. The signs resolved without intervention by day 10 post-application. The signs in this dog may have been related to peak serum levels of moxidectin, which vary between dogs, and occur between 1 and 21 days after application of imidacloprid and moxidectin topical solution.

The following clinical observations also occurred in laboratory effectiveness studies following application with imidacloprid and moxidectin topical solution and may be directly attributed to the drug or may be secondary to the intestinal parasite burden or other underlying conditions in the dogs: diarrhea, bloody stools, vomiting, anorexia, lethargy, coughing, ocular discharge and nasal discharge. Observations at the application sites included damp, stiff or greasy hair, the appearance of a white deposit on the hair, and mild erythema, which resolved without treatment within 2 to 48 hours.

Heartworm-Positive Dogs

Field Study: A 56-day field safety study was conducted in 214 *D. immitis* heartworm and microfilaria positive dogs with Class 1, 2 or 3 heartworm disease. All dogs received imidacloprid and moxidectin topical solution on Study Days 0 and 28; 108 dogs also received melarsomine dihydrochloride on Study Days -14, 14 and 15. All dogs were hospitalized for a minimum of 12 hours following each treatment. Effectiveness against circulating *D. immitis* microfilariae was > 90 % at five of six sites; however, one site had an effectiveness of 73.3 %. The microfilaria count in some heartworm-positive dogs increased or remained unchanged following treatment with imidacloprid and moxidectin topical solution alone or in a dosing regimen with melarsomine dihydrochloride.

Following treatment with imidacloprid and moxidectin topical solution alone or in a dosing regimen with melarsomine dihydrochloride, the following adverse reactions were observed:

Adverse Reaction	Dogs Treated with imidacloprid and moxidectin topical solution Only n=106	Dogs Treated with imidacloprid and moxidectin topical solution + Melarsomine n=108
Cough	24 (22.6 %)	25 (23.1 %)
Lethargy	14 (13.2 %)	42 (38.9 %)
Vomiting	11 (10.4 %)	18 (16.7 %)
Diarrhea, including hemorrhagic	10 (9.4 %)	22 (20.4 %)
Inappetence	7 (6.6 %)	19 (17.6 %)
Dyspnea	6 (5.7 %)	10 (9.3 %)
Tachypnea	1 (< 1 %)	7 (6.5 %)
Pulmonary Hemorrhage	0	5 (< 1 %)
Death	0	3 (2.8 %)

Three dogs treated with imidacloprid and moxidectin topical solution in a dosing regimen with melarsomine dihydrochloride died of pulmonary embolism from dead and dying heartworms. One dog, treated with imidacloprid and moxidectin topical solution and melarsomine dihydrochloride, experienced pulmonary hemorrhage and responded to supportive medical treatment. Following the first treatment with imidacloprid and moxidectin topical solution alone, two dogs experienced adverse reactions (coughing, vomiting, and dyspnea) that required hospitalization. In both groups, there were more adverse reactions to imidacloprid and moxidectin topical solution following the first treatment than the second treatment.

To report a suspected adverse reaction, call 1-800-338-3659.

Post-Approval Experience

The following adverse events are based on post-approval adverse drug experience reporting. 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 in dogs are listed in decreasing order of reporting frequency: depression/lethargy, vomiting, pruritus, diarrhea, anorexia, hyperactivity, ataxia, trembling, hypersalivation, application site reactions (alopecia, pruritus, lesions, and erythema), seizures, and anaphylaxis/anaphylactic reactions (hives, urticaria, facial swelling, edema of the head).

Serious reactions, including neurologic signs and death have been reported when cats have been exposed (orally and topically) to this product.

In humans, nausea, numbness or tingling of the mouth/lips and throat, ocular and dermal irritation, pruritus, headache, vomiting, diarrhea, depression and dyspnea have been reported following exposure to this product.

To report suspected adverse events and/or obtain a copy of the SDS or for technical assistance, call VIRBAC AH, Inc. at 1-800-338-3659.

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

DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin, once a month, by topical administration.

Do not apply to irritated skin.

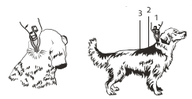
1. Use scissors to open the foil pack, taking care not to damage the tube inside. Remove one dose applicator tube from the package and hold the tube in an upright position. As specified in the following table, administer the entire contents of the PARASEDGE ™ Multi for Dogs (imidacloprid + moxidectin) tube that correctly corresponds with the body weight of the dog.

Dog (lbs.)	PARASEDGE™ Multi for Dogs	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
3 - 9	PARASEDGE™ Multi 9	0.4	40	10
9.1 - 20	PARASEDGE™ Multi 20	1.0	100	25
20.1 - 55	PARASEDGE™ Multi 55	2.5	250	62.5
55.1 - 88	PARASEDGE™ Multi 88	4.0	400	100
88.1 - 110*	PARASEDGE™ Multi 110	5.0	500	125

*Dogs over 110 lbs. should be treated with the appropriate combination of PARASEDGE™ Multi for Dogs tubes.

2. Bend the tip back until it snaps off. If it doesn't snap off at first, cut it using sossors.

3. The dog should be standing for application. Part the hair on the back of the dog between the shoulder blades until the skin is visible. For dogs weighing 20 lbs. or less, place the tip of the tube on the skin and apply the entire contents directly on the exposed skin at one spot between the shoulder blades. For dogs weighing more than 20 lbs., place the tip of the tube on the skin and apply the entire contents directly on the exposed skin at 3 or 4 spots on the top of the backline from the base of the neck to the upper back in an area inaccessible to licking. Do not apply an amount of solution at any one location that could run off the side of the dog.



4. Keep tube compressed on the final squeeze to avoid drawing liquid back into tube. While keeping tube squeezed, drag it away from liquid and lift up to remove.

5. Ensure tube is empty.

Do not let this product get in your dog's mouth or eyes. **Do not allow the dog to lick any of the application sites for 30 minutes.** In households with multiple pets, keep each treated dog separated from other treated dogs and other pets for 30 minutes after application to prevent licking the application sites. **(See WARNINGS.)**

Stiff hair, a damp appearance of the hair, pink skin, or a slight powdery residue may be observed at the application site on some animals. This is temporary and does not affect the safety and effectiveness of the product.

Shampooing 90 minutes after treatment does not reduce the effectiveness of PARASEDGE™ Multi for Dogs in the prevention of heartworm disease. Shampooing or water immersion 4 days after treatment will not reduce the effectiveness of PARASEDGE™ Multi for Dogs in the treatment of flea infestations. However, shampooing as often as once weekly may reduce the effectiveness of the product against fleas.

Heartworm Prevention: For prevention of heartworm disease, PARASEDGE™ Multi for Dogs should be administered at one-month intervals. PARASEDGE™ Multi for Dogs may be administered year-round or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer PARASEDGE™ Multi for Dogs immediately and resume the monthly dosing schedule. When replacing another heartworm preventative product in a heartworm prevention program, the first treatment with PARASEDGE™ Multi for Dogs should be given within one month of the last dose of the former medication.

Treatment of Circulating Microfilaria: For the treatment of circulating *D. immitis* microfilaria in heartworm-positive dogs, PARASEDGE™ Multi for Dogs should be administered at one-month intervals. Treatment with an approved adulticide therapy is recommended because PARASEDGE™ Multi for Dogs is not effective for the treatment of adult *D. immitis*. **(See PRECAUTIONS.)**

Flea Treatment: For the treatment of flea infestations, PARASEDGE™ Multi for Dogs should be administered at one-month intervals. If the dog is already infested with fleas when the first dose of PARASEDGE™ Multi for Dogs is administered, adult fleas on the dog will be killed. However, reinfestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated. Dogs treated with imidacloprid, including those with pre-existing flea allergy dermatitis have shown clinical improvement as a direct result of elimination of fleas from the dog.

Treatment and Control of Intestinal Nematode Infections:
For the treatment and control of intestinal hookworm infections caused by *Ancylostoma caninum* and *Uncinaria stenocephala* (adults, immature adults and fourth stage larvae) and roundworm infections caused by *Toxocara canis* (adults and fourth stage larvae), and *Toxascaris leonina* (adults), and whipworm infections caused by *Trichuris vulpis* (adults), PARASEDGE™ Multi for Dogs should be administered once as a single topical dose.

Treatment and Control of Sarcoptic Mange: For the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei var. canis*, PARASEDGE™ Multi for Dogs should be administered as a single topical dose. A second monthly dose may be administered if necessary.

ANIMAL SAFETY:

Heartworm-Negative Dogs

Field Study: In a controlled, double-masked, field safety study, imidacloprid and moxidectin topical solution was administered to 128 dogs of various breeds, 3 months to 15 years of age, weighing 4 to 157 pounds. Imidacloprid and moxidectin topical solution was used safely in dogs concomitantly receiving ACE inhibitors, anticonvulsants, antihistamines, antimicrobials, chondroprotectants, corticosteroids, immunotherapeutics, MAO inhibitors, NSAIDs, ophthalmic medications, sympathomimetics, synthetic estrogens, thyroid hormones, and urinary acidifiers. Owners reported the following signs in their dogs after application of imidacloprid and moxidectin topical solution: pruritus, flaky/greasy residue at the treatment site, medicinal odor, lethargy, inappetence, and hyperactivity. **(See ADVERSE REACTIONS.)**

Safety Study in Puppies: Imidacloprid and moxidectin topical solution was applied topically at 1, 3 and 5X the recommended dose to 7-week-old Beagle puppies once every 2 weeks for 6 treatments on days 0, 14, 28, 42, 56 and 70. Loose stools and diarrhea were observed in all groups, including the controls, throughout the study. Vomiting was seen in one puppy from the 1X treatment group (day 57), in two puppies from the 3X treatment group (days 1 and 79), and in one puppy from the 5X treatment group (day 1). Two puppies each in the 1X, 3X, and 5X groups had decreased appetites within 24 hours post-dosing. One puppy in the 1X treatment group had pruritus for one hour following the fifth treatment. A puppy from the 5X treatment group displayed rapid, difficult breathing from 4 to 8 hours following the second treatment.

Dermal Dose Tolerance Study: Imidacloprid and moxidectin topical solution was administered topically to 8-month-old Beagle dogs at 10X the recommended dose once. One dog showed signs of treatment site irritation after application. Two dogs vomited, one at 6 hours and one at 6 days post-treatment. Increased RBC, hemoglobin, activated partial thromboplastin, and direct bilirubin were observed in the treated group. Dogs in the treated group did not gain as much weight as the control group.

Oral Safety Study in Beagles: Imidacloprid and moxidectin topical solution was administered once orally at the recommended topical dose to 12 dogs. Six dogs vomited within 1 hour of receiving the test article, 2 of these dogs vomited again at 2 hours, and 1 dog vomited again up to 18 hours post-dosing. One dog exhibited shaking (nervousness) 1 hour post-dosing. Another dog exhibited abnormal neurological signs (circling, ataxia, generalized muscle tremors, and dilated pupils with a slow pupillary light response) starting at 4 hours post-dosing through 18 hours post-dosing. Without treatment, this dog was neurologically normal at 24 hours and had a normal appetite by 48 hours post-dosing. **(See CONTRAINDICATIONS.)**

Dermal Safety Study in Ivermectin-Sensitive Collies:
Imidacloprid and moxidectin topical solution was administered topically at 3 and 5X the recommended dose every 28 days for 3 treatments to Collies which had been pre-screened for avermectin sensitivity. No clinical abnormalities were observed.

Oral Safety Study in Ivermectin-Sensitive Collies:
Imidacloprid and moxidectin topical solution was administered orally to 5 pre-screened ivermectin-sensitive Collies. The Collies were asymptomatic after ingesting 10 % of the minimum labeled dose. At 40 % of the minimum recommended topical dose, 4 of the dogs experienced neurological signs indicative of avermectin toxicity including depression, ataxia, mydriasis, salivation, muscle fasciculation, and coma, and were euthanized. **(See CONTRAINDICATIONS.)**

Heartworm-Positive Dogs

Laboratory Safety Study in Heartworm-Positive Dogs: Imidacloprid and moxidectin topical solution was administered topically at 1 and 5X the recommended dose every 14 days for 3 treatments to dogs with adult heartworm infections and circulating microfilaria. At 5X, one dog was observed vomiting three hours after the second treatment. Hypersensitivity reactions were not seen in the 5X treatment group. Microfilaria counts decreased with treatment.

STORAGE INFORMATION: Store below 25°C (77°F).

HOW SUPPLIED:
Applications Per Package : 3 x 0.4 mL tubes, 3 x 1.0 mL tubes, 3 x 2.5 mL tubes, 3 x 4.0 mL tubes, 3 x 5.0 mL tubes

Approved by FDA under ANADA # 200-700

Manufactured for: Virbac AH, Inc., P.O. Box 162059, Fort Worth, TX 76161

LA20679

Rev. 10/2021

Virbac

PARASEDGE™ Multi for Cats
(imidacloprid + moxidectin)
Topical Solution

Once-a-month topical solution for cats for the prevention of heartworm disease, kills adult fleas, is indicated for the treatment of flea infestations, as well as the treatment and control of ear mite infestations and intestinal parasite infections in cats and kittens 9 weeks of age and older and that weigh at least 2 lbs.

Once-a-month topical solution for ferrets for the prevention of heartworm disease, kills adult fleas, and is indicated for the treatment of flea infestations. Indicated for ferrets that weigh at least 2 lbs.

CAUTION:
Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
PARASEDGE™ Multi for Cats (10% imidacloprid + 1% moxidectin) is a colorless to yellow ready-to-use solution packaged in single dose applicator tubes for topical treatment of cats. The formulation and dosage schedule are designed to provide a minimum of 4.5 mg/lb (10.0 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin based on body weight.

Imidacloprid is a chloronicotinyl nitroguanidine insecticide. The chemical name of imidacloprid is 1-[(6-Chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine. Moxidectin is a semisynthetic macrocyclic lactone endectocide derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus*. The chemical name of moxidectin is [6R, 23E, 25S(E)]-5-O-Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

INDICATIONS:
PARASEDGE Multi for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. PARASEDGE Multi for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. PARASEDGE Multi for Cats is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the following intestinal parasites:

Intestinal Parasite		Intestinal Stage		
		Adult	Immature Adult	Fourth Stage Larvae
Hookworm Species	*Ancylostoma tubaeforme*	X	X	X
Roundworm Species	*Toxocara cati*	X		X

WARNINGS:
Do not use on sick, debilitated, or underweight cats (See ADVERSE REACTIONS).
Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight.

HUMAN WARNINGS:
Not for human use. Keep out of the reach of children.
Children should not come in contact with the application site for 30 minutes after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headache; dizziness; and redness, burning, tingling, or numbness of the skin.
Wash hands thoroughly with soap and warm water after handling.
If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice.

The Safety Data Sheet (SDS) provides more detailed occupational safety information. To report suspected adverse drug events, for technical assistance or to obtain a copy of the SDS, contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

PRECAUTIONS:
Do not dispense dose applicator tubes without complete safety and administration information.

Avoid oral ingestion. Cats may experience hypersalivation, tremors, vomiting and decreased appetite if PARASEDGE Multi for Cats is inadvertently administered orally or through grooming/licking of the application site.

The safety of PARASEDGE Multi for Cats has not been established in breeding, pregnant, or lactating cats.

The effectiveness of PARASEDGE Multi for Cats against heartworm infections (*D. immitis*) after bathing has not been evaluated in cats.

Use of this product in geriatric patients with subclinical conditions has not been adequately studied. Several otherwise healthy, thin geriatric cats experienced prolonged lethargy and sleepiness after using this drug.

(See ADVERSE REACTIONS.)

ADVERSE REACTIONS:

Field Study: Following treatment with imidacloprid and moxidectin or an active control, cat owners reported the following post-treatment reactions:

OBSERVATION	Imidacloprid and moxidectin n=113	Active Control n = 38
Lethargy (protracted sleeping, poorly responsive)	3 cats* (2.7 %)	None observed
Behavioral changes (e.g., agitated, excessive grooming, hiding, pacing, spinning)	9 cats (8.0 %)	1 cat (2.6%)
Discomfort (e.g., scratching, rubbing, head-shaking)	5 cats (4.4 %)	None observed
Hypersalivation (within 1 hour after treatment)	3 cats (2.7 %)	None observed
Polydipsia	3 cats (2.7 %)	None observed
Coughing and gagging	1 cat (0.9 %)	None observed

*These three cats were from the same household and included one 13-yr-old cat in good health, one 15-yr-old FIV positive cat in good health, and one 15-yr-old, underweight cat in fair health. Lethargy was noted for 24 to 36 hrs after the first treatment only; one cat was unsteady at 48 hrs. These cats were not on other medications.

During another field study, a 16-year-old cat with renal disease slept in the same place without moving for two days following application.

(See PRECAUTIONS.)

Laboratory Effectiveness Studies: Imidacloprid and moxidectin was administered at the recommended dose to 215 cats in 20 effectiveness studies. One random-sourced cat exhibited signs consistent with either moxidectin toxicity or viral respiratory disease and died 26 hours after product application; necropsy findings were inconclusive as to the cause of death.
A second cat that became ill 3 days after application of imidacloprid and moxidectin responded to treatment for respiratory infection and completed the study. A third cat became ill on day 3 and died with signs and lesions attributable to panleukopenia on day 7 after moxidectin application.

Post-Approval Experience: The following adverse events are based on post-approval adverse drug experience reporting. 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 in cats are listed in decreasing order of reporting frequency: hypersalivation, depression/lethargy, application site reactions (alopecia, pruritus, lesions, and erythema), decreased appetite, vomiting, hyperactivity, ataxia, trembling, and behavior disorder (hiding).

In some cases death has been reported.

In humans, ocular and dermal irritation, nausea, numbness or tingling of the mouth and lips, anaphylaxis, pruritus, vomiting, and tongue/taste abnormalities have been reported following exposure to this product.

To report suspected adverse events and/or obtain a copy of the SDS or for technical assistance, call Virbac AH, Inc. at 1-800-338-3659. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

DOSAGE AND ADMINISTRATION:
The recommended minimum dose is 4.5 mg/lb (10.0 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin, once a month, by topical administration.

Do not apply to irritated skin.

As specified in the following table, administer the entire contents of the PARASEDGE Multi for Cats tube that correctly corresponds with the body weight of the cat.

Cat (lb.)	PARASEDGE Multi for Cats	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2 - 5	PARASEDGE MULTI 5	0.23	23	2.3
5.1 - 9	PARASEDGE MULTI 9	0.4	40	4
9.1 - 18*	PARASEDGE MULTI 18	0.8	80	8

* Cats over 18 lbs. should be treated with the appropriate combination of PARASEDGE Multi for Cats tubes.

Steps 1 and 2

1. Use scissors to open the foil pack, taking care not to damage the tube inside. Remove the tube from the foil pack and hold upright with the lot and expiration at the bottom.

2. Bend the tip back until it snaps off. If it doesn't snap off at first, cut it using scissors.

Steps 3 and 4

3. Part the hair on the back of the cat's neck at the base of the neck, in front of the shoulder blades, until the skin is visible.

4. Place the tip of the PARASEDGE Multi for Cats tube on the skin. Squeeze the tube firmly 3-4 times in one spot until empty. Keep tube compressed on the final squeeze to avoid drawing liquid back into the tube. Avoid contact between PARASEDGE Multi for Cats and your fingers.

Steps 5 and 6

5. While keeping tube squeezed, drag it away from liquid and lift up to remove.

6. Ensure tube is empty.

Do not get this product in the cat's mouth or eyes or allow the cat to lick the application site for 30 minutes. Treatment at the base of the head will minimize the opportunity for ingestion by grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.

Stiff, matted hair or a damp, oily appearance of the hair may be observed at the application site on some cats. This is temporary and does not affect the safety and effectiveness of the product.

Heartworm Prevention: For prevention of heartworm disease, PARASEDGE Multi for Cats should be administered at one-month intervals. PARASEDGE Multi for Cats may be administered year-around or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer PARASEDGE Multi for Cats immediately and resume the monthly dosing schedule. When replacing another heartworm preventative product in a heartworm prevention program, the first treatment with PARASEDGE Multi for Cats should be given within one month of the last dose of the former medication. At the discretion of the veterinarian, cats older than 6 months of age may be tested to determine the presence of existing heartworm infection before treatment with PARASEDGE Multi for Cats **(See ADVERSE REACTIONS – Post-Approval Experience).**

Flea Treatment: For the treatment of flea infestations, PARASEDGE Multi for Cats should be administered at one-month intervals. If the cat is already infested with fleas when the first dose of PARASEDGE Multi for Cats is administered, adult fleas on the cat will be killed. However, re-infestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated. Cats treated with imidacloprid, including those with pre-existing flea allergy dermatitis have shown clinical improvement as a direct result of elimination of fleas from the cat.

Ear Mite Treatment: For the treatment of ear mites (*Otodectes cynotis*), PARASEDGE Multi for Cats should be administered once as a single topical dose. Monthly use of PARASEDGE Multi for Cats will control any subsequent ear mite infestations.

Intestinal Nematode Treatment: For the treatment and control of intestinal hookworm infections caused by *Ancylostoma tubaeforme* (adults, immature adults and fourth stage larvae) and roundworm infections caused by *Toxocara cati* (adults and fourth stage larvae), PARASEDGE Multi for Cats should be administered once as a single topical dose.

(CONTINUED ON NEXT PAGE)

PRODUCT INSERTS/DISCLOSURES

(CONTINUED FROM PREVIOUS PAGE)

ANIMAL SAFETY:
Studies in Kittens: Imidacloprid and moxidectin was topically applied at 0, 1, 3, and 5X the maximum dose to 48 healthy 9-week-old kittens on days 0, 28, and 56.

Lethargy was observed in 1 kitten from the 3X group and 1 from the 5X group on the day after initial treatment; the kitten from the 3X group was also disoriented and ataxic. One kitten from the 3X group had a slow pupillary light response two days after treatment and one had tremors the day after treatment. Hypersalivation was seen in one kitten from the 5X group approximately six hours post-treatment. One kitten from the 3X group was scratching at the treatment site 2 days after treatment. Slight cough was noted in 7 different kittens (2-0X, 2-1X, and 3-5X) during the 13-day period following the first treatment. Histopathology showed granulomatous inflammation at the treatment site in three 1X kittens. Causal relationship to the drug could not be determined. Pulmonary inflammation (1-5X) and lymphoid hyperplasia (2-1X, 4-3X) were seen in treated kittens. In a second study, imidacloprid and moxidectin was topically applied at 0, 1.7, 5.2 and 8.7X the maximum dose to 48 healthy 9-week-old kittens every two weeks for 6 doses. One kitten in the 8.7X group apparently ingested an unknown amount of the drug and developed the following clinical signs prior to euthanasia: mydriasis, salivation, depression, vomiting, unsteadiness, rapid to slow to difficult breathing, poor pupillary response, generalized tremors, inability to move, and nystagmus. Two kittens in the 5.2X group developed mydriasis, salivation, depression, squinting, and poor appetite. A kitten in the 1.7X group developed mydriasis.

Dose Tolerance Study: Eight healthy juvenile cats were topically dosed with a single application of imidacloprid and moxidectin at 10 times the recommended dose volume.
Mild, transient hypersalivation occurred in two of the cats.

Oral Study in Cats: The oral safety of imidacloprid and moxidectin was tested in case of accidental oral ingestion. The maximum topical dose was orally administered to twelve healthy 9-week-old kittens. Hypersalivation (8 of 12 kittens) and vomiting (12 of 12 kittens) were observed immediately post-treatment. Tremors developed in one kitten within 1 hour, resolving without treatment within the next hour. All 12 kittens were either anorexic or had decreased appetite for at least 1 day following treatment. In 3 kittens, the anorexia or decreased appetite continued into the second week following treatment. There was a post-treatment loss of body weight in treated kittens compared to control kittens. In a pilot safety study using kittens younger in age and lighter in weight than allowed by product labeling, an 8-week old kitten weighing 0.6 kg orally received 2X of the label topical dose (0.46 mL/kg). Immediately after dosing, it vomited, had labored breathing and slight tremors. Within 4 hours, it was normal, but was found dead on day 6. Necropsy could not determine the cause of death.

Study in Heartworm Positive Cats: Young adult cats were inoculated subcutaneously with third-stage *D. Immitis* larvae. At 243-245 days post-infection, immunoserology and echocardiography were performed to identify cats with adult heartworm burdens similar to naturally-acquired infections. Two groups were treated topically with either imidacloprid and moxidectin at the label dose or placebo, once every 28 days, for three consecutive treatments. A third group was treated topically, once, with imidacloprid and moxidectin at 5X the label dose. Sporadic vomiting and labored breathing related to heartworm burden were observed in the treatment and control groups. There was no difference between treatment groups in the numbers of adult *D. immitis* recovered at study conclusion. No adverse reactions were associated with the topical application of imidacloprid and moxidectin to experimentally heartworm-infected cats.

FERRETS

Use only the 0.4 mL PARASEDGE Multi for Cats in ferrets. The 0.23 mL size does not provide an effective dose and the 0.8 mL size could result in an overdose.

INDICATIONS:
For ferrets:
PARASEDGE Multi for Cats is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. PARASEDGE Multi for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations on ferrets.

WARNINGS:
Do not use on sick or debilitated ferrets.

PRECAUTIONS:
Do not dispense dose applicator tubes without complete safety and administration information.

The safety of PARASEDGE Multi for Cats has not been established in breeding, pregnant, and lactating ferrets.

Treatment of ferrets weighing less than 2.0 lbs (0.9 kg) should be based on a risk-benefit assessment.

The effectiveness of PARASEDGE Multi for Cats in ferrets weighing over 4.4 lbs (2.0 kg) has not been established.

ADVERSE REACTIONS:
Field Safety Study in Ferrets: Imidacloprid and moxidectin was topically administered to 131 client-owned ferrets at the recommended dose volume (0.4 mL). The ferrets ranged in age from 3 months to 7 years, and weighed between 0.5 and 1.86 kg (1.1 to 4.1 lbs). The dose of imidacloprid ranged between 21.5 to 80.2 mg/kg in this study. The dose of moxidectin ranged between 2.2 to 8.0 mg/kg in this study.

Adverse reactions in ferrets following treatment included: pruritus/scratching, scabbing, redness, wounds and inflammation at the treatment site; lethargy; and chemical odor. These adverse reactions resolved without additional therapy. Owners also reported stiffening of the hair at the treatment site, however, this is expected with application of a topical product and is not considered an adverse reaction.

Three human adverse reactions were reported. An owner's finger became red following skin contact with the product. One owner reported a headache caused by the chemical odor of the product. One owner reported a tingling sensation of the lips after kissing the treatment site.

Foreign Market Experience: Because the following events were reported voluntarily during post-approval use of the product in foreign markets, it is not always possible to reliably establish a causal relationship to drug exposure.

Adverse events reported in ferrets topically treated with 0.4 mL imidacloprid + moxidectin for cats included: malaise, vomiting, diarrhea, shaking, mydriasis, hypersalivation with abnormal neurologic signs, seizures, death, generalized hematoma of the body, and alopecia at the treatment site. Adverse reactions in humans included: burning, tingling, numbness, bad taste in the mouth, dizziness, and headache.

ANIMAL SAFETY:
Ferrets: Imidacloprid and moxidectin was topically applied at 5X the recommended dose volume to six healthy 9-month-old ferrets on Study Days 0, 14, 28, and 42. Because the weights of the ferrets in this study ranged from 2.0 to 4.0 lb (0.9 kg to 1.8 kg), ferrets received a range of dosages from 51.0 to 106.9 mg/lb (112 to 235 mg/kg) of imidacloprid and 5 to 10.5 mg/lb (11 to 23 mg/kg) of moxidectin. The following abnormal clinical signs were reported during the study: wet, matted, and/or greasy appearance to the hair, shaking of the head and/or body, rubbing of dose site on cage, and shedding. Slight increases in phosphorous, potassium, aspartate aminotransferase (AST), and glucose were seen during the study, however, no clinical signs related to these bloodwork changes were reported.

Oral Safety Study: Imidacloprid and moxidectin was orally administered at the recommended dose volume (0.4 mL) to eight healthy ferrets on Study Day 0. Ferrets were 78 to 101 days old (11.1 to 14.4 weeks) and weighed between 1.1 to 1.8 lb (0.5 to 0.8 kg) body weight on the day of dosing, resulting in doses ranges of 22.0–36.8 mg/lb (48.3–81.0 mg/kg) imidacloprid and 2.2–3.7 mg/lb (4.8–8.0 mg/kg) moxidectin. The following abnormal clinical signs were reported immediately following oral administration of imidacloprid and moxidectin: vomiting (one ferret) and ataxia (two ferrets). All abnormalities resolved without treatment or supportive care.

DOSAGE AND ADMINISTRATION:
For ferrets:
The recommended minimum dose for a ferret is 9 mg/lb (20 mg/kg) imidacloprid and 0.9 mg/lb (2 mg/kg) moxidectin, once a month, by topical administration.

Ferret (lbs.)	PARASEDGE Multi for Cats	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2.0 - 4.4	PARASEDGE MULTI 9	0.4	40	4

Only the 0.4 mL applicator tube volume (PARASEDGE Multi 9) should be used on ferrets.

Do not apply to irritated skin.


Steps 1 and 2

1. Use scissors to open the foil pack, taking care not to damage the tube inside. Remove the tube from the foil pack and hold upright with the lot and expiration at the bottom.

2. Bend the tip back until it snaps off. If it doesn't snap off at first, cut it using scissors.


Steps 3 and 4

3. Part the hair on the back of the ferret's neck at the base of the neck, in front of the shoulder blades until the skin is visible.

4. Place the tip of the PARASEDGE Multi for Cats tube on the skin. Squeeze the tube firmly 3-4 times in one spot until empty. Keep tube compressed on the final squeeze to avoid drawing liquid back into the tube. Avoid contact between PARASEDGE Multi for Cats and your fingers.


Steps 5 and 6

5. While keeping tube squeezed, drag it away from liquid and lift up to remove.

6. Ensure tube is empty.

Do not get this product in the ferret's mouth or eyes or allow the ferret to lick the application site for 30 minutes. Treatment at the base of the head will minimize the opportunity for ingestion by grooming. In households with multiple pets, keep animals separated to prevent licking of the application site.

Stiff, matted hair or a damp, oily appearance of the hair may be observed at the application site on some ferrets. This is temporary and does not affect the safety or effectiveness of the product.

Heartworm Prevention: For prevention of heartworm disease, PARASEDGE Multi for Cats should be administered at one-month intervals. PARASEDGE Multi for Cats may be administered year-round or at a minimum should start one month before the first expected exposure to mosquitoes and should continue at monthly intervals until one month after the last exposure to mosquitoes. If a dose is missed and a 30-day interval between doses is exceeded, administer PARASEDGE Multi for Cats immediately and resume the monthly dosing schedule.

Flea Treatment: For the treatment of flea infestations on ferrets, PARASEDGE Multi for Cats should be administered at one-month intervals. If the ferret is already infested with fleas when the first dose of PARASEDGE Multi for Cats is administered, adult fleas on the ferret will be killed. However, re-infestation from the emergence of pre-existing pupae in the environment may continue to occur for six weeks or longer after treatment is initiated.

STORAGE INFORMATION:
Store below 25°C (77°F).

HOW SUPPLIED:
Applications Per Package
3 x 0.23 mL tubes
3 x 0.4 mL tubes
3 x 0.8 mL tubes

Approved by FDA under ANADA # 200-701

Manufactured for: Virbac AH, Inc.,
P.O. Box 162059, Fort Worth, TX 76161

02 - 04/22
LB20219

RILEXINE®
(cephalexin tablets)
Chewable Tablets

Antimicrobial for Oral Use in Dogs only

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

DESCRIPTION: RILEXINE chewable tablets are a chewable, bisected tablet supplied in 3 sizes containing 150 mg, 300 mg, and 600 mg of cephalexin. Cephalexin is a cephalosporin, beta-lactam, broad spectrum antibiotic. The full chemical name for cephalexin is 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate.

INDICATION: For the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *Staphylococcus pseudintermedius*.

DOSAGE AND ADMINISTRATION: The recommended dose is 22 mg/kg (10 mg/lb) of body weight twice daily for 28 days.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to cephalexin. Therapy with RILEXINE chewable tablets may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly. If acceptable response to treatment is not observed, then the diagnosis should be re-evaluated and appropriate alternative therapy considered.

CONTRAINDICATIONS: RILEXINE chewable tablets are contraindicated in dogs with a known allergy to cephalexin or to the β-lactam (any of the penicillins or cephalosporins) group of antibiotics.

WARNINGS: For use in dogs only. Not for use in humans. Keep this drug out of the reach of children. Antimicrobials, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. Sensitized individuals handling such antimicrobials, including cephalexin, should avoid contact of the product with the skin and mucous membranes in order to minimize the risk of allergic reactions.

In case of ingestion by humans contact a physician immediately. Physicians may contact a poison control center for advice concerning cases of ingestion by humans.

PRECAUTIONS: Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant animal pathogens.

RILEXINE chewable tablets are designed to taste good. **Store RILEXINE chewable tablets out of reach of dogs, cats, and other pets in a secured location.** Post approval experience has shown that dogs and cats may willingly consume more than the recommended dosage of RILEXINE chewable tablets, which can result in overdose. Adverse reactions may occur if large quantities of tablets are ingested (see **Adverse Reactions, Animal Safety,** and **Information for Dog Owners** sections). If the product is dispensed in a container other than the original, prescribers should consider adding a statement on the bottle label reminding the owner that RILEXINE chewable tablets are designed to taste good and should be stored out of reach of pets in a secured location.

The safe use of RILEXINE chewable tablets in dogs intended for breeding and in pregnant or lactating bitches has not been evaluated.

Positive direct Coombs' test results and false positive reactions for glucose in the urine have been reported during treatment with some cephalosporin antimicrobials. Cephalosporin antimicrobials may also cause falsely elevated urine protein determinations. Some antimicrobials, including cephalosporins, can cause lowered albumin values due to interference with certain testing methods.

Occasionally, cephalosporins have been associated with myelotoxicity, thereby creating a toxic neutropenia.[1] Other hematological reactions observed with cephalosporin therapy include neutropenia, anemia, hypoprothrombinemia, thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), platelet dysfunction, and transient increases in serum aminotransferases.[2]

ADVERSE REACTIONS: The most common adverse reactions in dogs include diarrhea, vomiting, anorexia and lethargy.

A total of 211 dogs were included in the field study safety analysis. Adverse reactions reported in dogs treated with RILEXINE chewable tablets and placebo are summarized in Table 1.

Table1: Number of Adverse Reactions* Reported During the Field Study with RILEXINE chewable tablets

ADVERSE REACTION	RILEXINE chewable tablets n = 145	Placebo n = 66
Number of dogs with adverse reactions*	50 (34%)	22 (33%)
	# of Each Event*	# of Each Event*
Vomiting	29	9
Diarrhea	19	6
Anorexia	13	2
Lethargy	9	3
Pruritus	5	0
Dermatitis	4	3
Skin Lesions	5	1
Otitis Externa	4	2
Polydipsia	2	2
Somnolence	2	0
Flatulence	1	1
Tachypnea	1	1

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

No clinically significant differences were observed in the mean values for all laboratory tests including urinalysis between RILEXINE chewable tablets and placebo-treated dogs. At the end of treatment, group means for neutrophils, WBC, and globulin values were significantly higher in the placebo group than in the RILEXINE chewable tablets group; whereas, group mean values for eosinophils, A/G Ratio values, and total protein values were significantly higher in the RILEXINE chewable tablets group than in the placebo group. For all six of these parameters, the differences were not clinically significant and the mean values for each of the parameters remained within the normal range.

To report suspected adverse drug events or for technical assistance contact Virbac AH, Inc. at 1-800-338-3659. Visit us.virbac.com for product details. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

INFORMATION FOR DOG OWNERS: Owners should be advised that RILEXINE chewable tablets are designed to taste good. Owners should be instructed to keep the product in a secured storage area out of the reach of pets in order to prevent accidental ingestion or overdose. Post approval experience has shown that dogs and cats may willingly consume more than the recommended dosage of RILEXINE chewable tablets. Adverse reactions may occur if large quantities of tablets are ingested (see **Precautions, Adverse Reactions,** and **Animal Safety** sections).

Owners should be advised to contact their veterinarian immediately if the dog ingests more tablets than prescribed or if other pets ingest RILEXINE chewable tablets. In the case of accidental ingestion by humans, contact a physician immediately.

CLINICAL PHARMACOLOGY: Cephalexin belongs to the cephalosporin family of bactericidal antibiotics.

Cephalexin is readily and almost completely absorbed following oral administration (90% absolute bioavailability). Blood concentrations are proportional to dose within the range of at least 15 to 45 mg/kg. Binding to canine plasma proteins is low, ranging from 9 to 13% for cephalexin concentrations of 0.5 to 100 µg/mL.

Food reduces the peak cephalexin concentrations but has negligible effect on the extent of absorption.

A summary of the pharmacokinetics (PK) observed in fed and fasted Beagle dogs administered a single 22 mg/kg dose is provided in Table 2.

Table 2: Pharmacokinetics Parameter values (mean ± standard deviation), protein-corrected in fasted and fed dogs following a single administration of 22 mg/kg dose of RILEXINE chewable tablets (N = 12)

Parameter	FASTED Mean ± SD[1]	FED Mean ± SD[1]
AUCINF_obs (mg·h/L)	105.36 ± 17.31	108.35 ± 25.85
AUClast (mg·h/L)	97.33 ± 13.18	95.19 ± 11.84
Cmax (mg/L)	21.66 ± 2.74	16.99 ± 2.71
$T_{1/2}$ (h)	7.33 ± 4.30	8.79 ± 6.44
Tmax (h)	1.42 ± 0.42	1.17 ± 0.25

[1]SD = Standard Deviation

Cephalosporins are associated with time dependent killing effects. Accordingly, the pharmacodynamic (PD) target is time above MIC (T>MIC). For staphylococcal infections, the goal for time above MIC is 40% of the dosing interval (which translates to 4.8 hrs for a BID dosing schedule). For streptococcal infections, the target for time above MIC is 60% of the dosing interval (i.e., 7.2 hrs). To assess whether or not the PK-PD target is met with a 22mg/kg BID dosing regimen under fed and fasted conditions, it was assumed that the MIC$_{90}$ for *S.pseudintermedius* is 2µg/mL. Plasma drug concentrations were normalized to exactly 22mg/kg dose and corrected for 10% protein binding (protein binding observed in canine plasma).

Under fasted conditions, all targets were met in all dogs after the first daily dose. With food, the target for *S. aureus* was met by the second daily dose. Therefore, a 22 mg/kg BID dosing interval under fed or fasted conditions succeeded in attaining the PK-PD targets.

MICROBIOLOGY: Cephalexin is a cephalosporin antibiotic. Like other β-lactam antimicrobials, cephalexin exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial wall. Minimum Inhibitory Concentrations (MICs) for cephalexin against label-claim pathogens isolated from canine pyoderma in a 2008-2009 U.S. field trial are presented in Table 3. All MICs were determined in accordance with the Clinical Laboratory Standards Institute (CLSI) standards.

Table 3: Summary of Cephalexin MIC values against *S. pseudintermedius* isolates from 88 dogs treated with RILEXINE® (cephalexin tablets) Chewable Tablets for bacterial pyoderma in a U.S. field study during 2008-2009

Microbial Treatment Outcome	Time of Sampling	MIC$_{50}$ µg/mL	MIC$_{90}$ µg/mL	MIC Range µg/mL
Success (n = 61) *	Pre-treatment	1	2	1-2
Failure (n = 27) **	Pre-treatment	1	2	1-8
	Post-treatment (n = 17)	2	16	1-32

*No post-treatment sampling was conducted due to the absence of lesions.
**Of the 27 failures, 10 did not have positive post-treatment cultures.

EFFECTIVENESS: The clinical effectiveness of RILEXINE chewable tablets was established in a randomized, multi-location, placebo-controlled field study (see Table 4). In this study, 131 dogs with secondary superficial bacterial pyoderma treated with either RILEXINE chewable tablets (n = 91) at 22 mg/kg (10 mg/lb) body weight or with a negative control (n = 40), twice daily for 28 days, were analyzed. RILEXINE chewable tablets were considered superior to the placebo (70% success rate vs. 13% respectively) in the treatment of secondary superficial bacterial pyoderma caused by susceptible strains of *S.pseudintermedius*.

Table 4: Primary endpoint: Percentage of Cure* in the Effectiveness population

Treatment	RILEXINE chewable tablets	Placebo	p-value
N	91	40	
Success	64 (70.3%)	5 (12.5%)	0.0009
Failures	27	35	

*Absence of lesions at the end of the study.

PALATABILITY: The palatability of RILEXINE chewable tablets was evaluated in two separate multi-location studies. In the first study, 39 client-owned dogs were dosed with RILEXINE chewable tablets at 22mg/kg and evaluated for palatability of the product. Palatability testing was performed twice daily prior to feeding for 7 days. Dogs freely consumed (from empty bowl or open hand) 80.8% of their doses. In a second study, 64 client-owned dogs enrolled in the field efficacy study were evaluated in a similar manner and freely consumed 78.4% of their doses.

ANIMAL SAFETY: RILEXINE chewable tablets were administered orally three times a day to 12-week-old healthy Beagles at 0 mg/kg (placebo), 22 mg/kg (1X), 66 mg/kg (3X), and 110 mg/kg (5X) for 12 weeks, and at 22 mg/kg twice a day for 12 weeks. The most common clinical findings included epiphora, salivation, vomiting and diarrhea among all the dose groups. Three dogs had decreased activity (1 in each from the 22 mg/kg twice a day, 22 mg/kg three times a day, and the 66 mg/kg three times a day groups). These observations were mild and sporadic.

There were increases in alanine aminotransferase (ALT) in the 110 mg/kg three times a day group and in the 22 mg/kg twice a day group that increased in a dose-dependent pattern. There was an increase in sorbitol dehydrogenase (SDH) in the 110 mg/kg three times a day group compared to the controls. These changes were minimal and the values remained within expected historical control ranges. There were several decreases in total protein (in the 110 mg/kg three times a day group) and/or globulin (in the 22, 66, and 110 mg/kg three times a day groups) compared to the controls. These changes resulted in occasional increases in albumin/globulin ratios. Although a drug effect cannot be ruled out, these changes were not clinically relevant.

A mild prolongation in prothrombin time (PT) was observed in the 22 mg/kg three times a day group. This was not considered clinically relevant due to the small change that remained within the reference ranges.

One dog in the 110 mg/kg three times a day group had moderate amounts of bilirubinuria at the Week 8 and Week 12 samplings. No clinical significance was noted.

Cephalexin was not present in any Day 1 samples prior to dosing or in any control animals. After dosing, cephalexin was well absorbed into systemic circulation of the treated dogs. Within gender and dosage level, Week 8 mean trough concentrations were generally higher than the Week 4 and 12 mean trough concentrations (between a 0.9 and 3.6-fold difference). The geometric mean plasma cephalexin trough concentration following three times daily administration of the 110 mg/kg dose was 11.2 µg/mL compared to 2.6 µg/mL and 8.7 µg/mL following 22 mg/kg and 66 mg/kg, respectively at Week 12. Geometric mean plasma cephalexin trough concentrations following administration of 22 mg/kg twice daily were 0.7, 1.3, and 1.0 µg/mL at Weeks 4, 8, and 12, respectively.

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

HOW SUPPLIED: RILEXINE® (cephalexin tablets) Chewable Tablets are supplied in 150 mg, 300 mg, and 600 mg tablets packaged in bottles of 100 tablets.

Approved by FDA under NADA # 141-326

Manufactured by: Virbac AH, Inc.
Fort Worth, TX 76161 USA

150 mg 07620 302054-06, 300 mg 07630 302055-06, 600 mg 07640 302056-06; Rev. date 01/2024

[1]Birchard SJ and Sherding RG. Saunders
Manual of Small Animal Practice, 2nd edition.
W.B. Saunders Co. 2000: p. 166.

[2]Adams HR. *Veterinary Pharmacology and Therapeutics*, 8th edition, 2001, p. 825.

SENERGY™ (selamectin)
Topical Parasiticide For Dogs and Cats

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

DESCRIPTION:
SENERGY (selamectin) Topical Parasiticide is available as a colorless to yellow, ready to use solution in single dose tubes for topical (dermal) treatment of dogs six weeks of age and older and cats eight weeks of age and older. The content of each tube is formulated to provide a minimum of 2.7 mg/lb (6 mg/kg) of body weight of selamectin. The chemical composition of selamectin is (5Z,25S)-25-cyclohexyl-4′-*O*-de(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-5-demethoxy-25-de(1-methylpropyl)-22, 23-dihydro-5-hydroxyiminoavermectin A_{1a}.

INDICATIONS:
SENERGY is recommended for use in dogs six weeks of age or older and cats eight weeks of age and older for the following parasites and indications:

Dogs:
SENERGY kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. SENERGY also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) and for the control of tick infestations due to *Dermacentor variabilis*.

Cats:
SENERGY kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. SENERGY is also indicated for the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections in cats.

WARNINGS:
Not for human use. Keep out of the reach of children.
In humans, SENERGY may be irritating to skin and eyes.
Reactions such as hives, itching and skin redness have been reported in humans in rare instances. Individuals with known hypersensitivity to SENERGY should use the product with caution or consult a health care professional. SENERGY contains isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water. In case of ingestion by a human, contact a physician immediately. The safety data sheet (SDS) provides more detailed occupational safety information. To report suspected adverse drug events, for technical assistance or to obtain a copy of the SDS, contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com.

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

Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

Do not use in sick, debilitated or underweight animals (see SAFETY).

PRECAUTIONS:
Prior to administration of SENERGY, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. Selamectin is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, selamectin is not effective for microfilariae clearance.

Hypersensitivity reactions have not been observed in dogs with patent heartworm infections administered three times the recommended dose of selamectin. Higher doses were not tested.

ADVERSE REACTIONS:
Pre-approval clinical trials:
Following treatment with selamectin, transient localized alopecia with or without inflammation at or near the site of application was observed in approximately 1% of 691 treated cats. Other signs observed rarely (≤0.5% of 1743 treated cats and dogs) included vomiting, loose stool or diarrhea with or without blood, anorexia, lethargy, salivation, tachypnea, and muscle tremors.

Post-approval experience:
In addition to the aforementioned clinical signs that were reported in pre-approval clinical trials, there have been reports of pruritus, urticaria, erythema, ataxia, fever, and rare reports of death. There have also been rare reports of seizures in dogs (see **WARNINGS**).

DOSAGE:
The recommended minimum dose is 2.7 mg selamectin per pound (6 mg/kg) of body weight.

Administer the entire contents of a single dose tube (or two tubes used in combination for dogs weighing over 130 pounds) of SENERGY topically in accordance with the following tables. (See **ADMINISTRATION** for the recommended treatment intervals.)

Cats (lb)	Package Color	mg per tube	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1–15	Blue	45 mg	60	0.75
15.1–22	Taupe	60 mg	60	1.0

For cats over 22 lbs use the appropriate combination of tubes.

Dogs (lb)	Package Color	mg per tube	Potency (mg/mL)	Administered volume (mL)
Up to 5	Mauve	15 mg	60	0.25
5.1–10	Lavender	30mg	120	0.25
10.1–20	Brown	60 mg	120	0.5
20.1–40	Red	120 mg	120	1.0
40.1–85	Teal	240 mg	120	2.0
85.1–130	Plum	360 mg	120	3.0

For dogs over 130 lbs use the appropriate combination of tubes. Recommended for use in dogs 6 weeks of age and older and in cats 8 weeks of age and older.

ADMINISTRATION:
A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying SENERGY topically to dogs and cats prior to first use. Remove the tube from the package and hold upright with the lot and expiration at the bottom. Bend the tip back until it snaps off. To administer the product, part the hair on the back of the animal at the base of the neck in front of the shoulder blades until the skin is visible. Place the tip of the tube on the skin and squeeze the tube 3 or 4 times to empty its entire contents directly onto the skin in one spot. Keeping the tube squeezed, drag it away from the liquid and lift to remove. Check the tube to ensure that it is empty. Do not massage the product into the skin. Due to alcohol content, do not apply to broken skin. Avoid contact between the product and fingers. Do not apply when the haircoat is wet. Bathing or shampooing the dog 2 or more hours after treatment will not reduce the effectiveness of SENERGY against fleas or heartworm. Bathing or shampooing the cat 2 hours after treatment will not reduce the effectiveness of SENERGY against fleas. Bathing or shampooing the cat 24 hours after treatment will not reduce the effectiveness of SENERGY against heartworm. Stiff hair, clumping of hair, hair discoloration, or a slight powdery residue may be observed at the treatment site in some animals. These effects are temporary and do not affect the safety or effectiveness of the product. Discard empty tubes in your ordinary household refuse.

Flea Control in Dogs and Cats
For the prevention and control of flea infestations, SENERGY should be administered at monthly intervals throughout the flea season, starting one month before fleas become active. In controlled laboratory studies >98% of fleas were killed within 36 hours. Results of clinical field studies using selamectin monthly demonstrated >90% control of flea infestations within 30 days of the first dose. Dogs and cats treated with selamectin, including those with pre-existing flea allergy dermatitis, showed improvement in clinical signs associated with fleas as a direct result of eliminating the fleas from the animals and their environment.

If the dog or cat is already infested with fleas when the first dose of selamectin is administered, adult fleas on the animal are killed and no viable fleas hatch from eggs after the first administration. However, an environmental infestation of fleas may persist for a short time after beginning treatment with selamectin because of the emergence of adult fleas from pupae.

Heartworm Prevention in Dogs and Cats
For the prevention of heartworm disease, SENERGY must be administered on a monthly basis. SENERGY may be administered year-round or at least within one month after the animal's first exposure to mosquitoes and monthly thereafter until the end of the mosquito season. The final dose must be given within one month after the last exposure to mosquitoes. If a dose is missed and a monthly interval between dosing is exceeded then immediate administration of SENERGY and resumption of monthly dosing will minimize the opportunity for the development of adult heartworms. When replacing another heartworm preventive product in a heartworm disease prevention program, the first dose of SENERGY must be given within a month of the last dose of the former medication.

Selamectin, the active ingredient in SENERGY, is a macrocyclic lactone compound. These compounds effectively prevent the development of adult heartworms when administered to dogs and cats within one month of exposure to infective (L_3) *Dirofilaria immitis* larvae. Efficacy of macrocyclic lactones decreases below 100% in dogs, however, if first administered >2 months after exposure to infective larvae. Thus, in heartworm endemic regions, delaying initiation of heartworm prevention using SENERGY beyond 2 months of first exposure to infective larvae (e.g., starting puppies and kittens at >8 weeks of age), or gaps of >2 months in the administration of SENERGY during periods of heartworm transmission, increases the risk of the animal acquiring heartworms. Animals with unknown heartworm history that test negative for heartworms prior to the initiation of SENERGY may be harboring pre-patent infections at the time SENERGY was started. Testing such animals 3–4 months after initiation of SENERGY would be necessary to confirm their negative heartworm status.

At the discretion of the veterinarian, cats ≥6 months of age may be tested to determine the presence of existing heartworm infections before beginning treatment with SENERGY. Cats already infected with adult heartworms can be given SENERGY monthly to prevent further infections.

Ear Mite Treatment in Dogs and Cats
For the treatment of ear mite (*O. cynotis*) infestations in dogs and cats, SENERGY should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of SENERGY will control any subsequent ear mite infestations. In the clinical field trials ears were not cleaned, and many animals still had debris in their ears after the second dose. Cleansing of the infested ears is recommended to remove the debris.

Sarcoptic Mange Treatment in Dogs
For the treatment of sarcoptic mange (*S. scabiei*) in dogs, SENERGY should be administered once as a single topical dose. A second monthly dose may be required in some dogs. Monthly use of SENERGY will control any subsequent sarcoptic mange mite infestations. Because of the difficulty in finding sarcoptic mange mites on skin scrapings, effectiveness assessments also were based on resolution of clinical signs. Resolution of the pruritus associated with the mite infestations was observed in approximately 50% of the dogs 30 days after the first treatment and in approximately 90% of the dogs 30 days after the second monthly treatment.

Tick Control in Dogs
For the control of tick (*Dermacentor variabilis*) infestations in dogs, SENERGY should be administered on a monthly basis. In heavy tick infestations, complete efficacy may not be achieved after the first dose. In these cases, one additional dose may be administered two weeks after the previous dose, with monthly dosing continued thereafter.

Nematode Treatment in Cats
For the treatment and control of intestinal hookworm (*A. tubaeforme*) and roundworm (*T. cati*) infections, SENERGY should be applied once as a single topical dose.

SAFETY:
Selamectin has been tested safe in over 100 different pure and mixed breeds of healthy dogs and over 15 different pure and mixed breeds of healthy cats, including pregnant and lactating females, breeding males and females, puppies six weeks of age and older, kittens eight weeks of age and older, and avermectin-sensitive collies. A kitten, estimated to be 5–6 weeks old (0.3 kg), died 8 1/2 hours after receiving a single treatment of selamectin at the recommended dosage. The kitten displayed clinical signs which included muscle spasms, salivation and neurological signs. The kitten was a stray with an unknown history and was malnourished and underweight (see **WARNINGS**).

DOGS: In safety studies, selamectin was administered at 1, 3, 5, and 10 times the recommended dose to six-week-old puppies, and no adverse reactions were observed. The safety of selamectin administered orally also was tested in case of accidental oral ingestion. Oral administration of selamectin at the recommended topical dose in 5- to 8-month-old beagles did not cause any adverse reactions. In a pre-clinical study selamectin was dosed orally to ivermectin-sensitive collies. Oral administration of 2.5, 10, and 15 mg/kg in this dose escalating study did not cause any adverse reactions; however, eight hours after receiving 5 mg/kg orally, one avermectin-sensitive collie became ataxic for several hours, but did not show any other adverse reactions after receiving subsequent doses of 10 and 15 mg/kg orally. In a topical safety study conducted with avermectin-sensitive collies at 1, 3 and 5 times the recommended dose of selamectin, salivation was observed in all treatment groups, including the vehicle control. Selamectin also was administered at 3 times the recommended dose to heartworm infected dogs, and no adverse effects were observed.

CATS: In safety studies, selamectin was applied at 1, 3, 5, and 10 times the recommended dose to six-week-old kittens. No adverse reactions were observed. The safety of selamectin administered orally also was tested in case of accidental oral ingestion. Oral administration of the recommended topical dose of selamectin to cats caused salivation and intermittent vomiting. Selamectin also was applied at 4 times the recommended dose to patent heartworm infected cats, and no adverse reactions were observed.

In well-controlled clinical studies, selamectin was used safely in animals receiving other frequently used veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, steroids, collars, shampoos and dips.

STORAGE CONDITIONS: Store below 25°C (77°F).

HOW SUPPLIED: Available in eight separate dose strengths for dogs and cats of different weights (see **DOSAGE**). SENERGY for puppies and kittens is available in cartons containing 3 single dose tubes. SENERGY for cats and dogs is available in cartons containing 3 single dose tubes.

Virbac SENERGY™ (selamectin)

Distributed by:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161

Approved by FDA under ANADA # 200-670

LA13661

PRODUCT INSERTS/DISCLOSURES

STELFONTA® (tigilanol tiglate injection) 1 mg/mL

Virbac

For intratumoral injection in dogs only
Antineoplastic
Single use vial

WARNING: SEVERE WOUND FORMATION IN HUMANS; EXTENSIVE WOUND FORMATION, MAST CELL DEGRANULATION, AND DEATH IN DOGS DUE TO MAST CELL DEGRANULATION

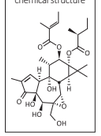
Human Safety
- **Accidental self-injection of STELFONTA® may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary (see Dosage and Administration, Human Warnings, and Adverse Reactions).**

Dog Safety
- **Always administer a corticosteroid (e.g. prednisone or prednisolone), an H1 receptor blocking agent (e.g. diphenhydramine), and an H2 receptor blocking agent (e.g. famotidine) when treating with STELFONTA to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation (see Contraindications and Dosage and Administration).**
- **Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see Contraindications, Warnings and Adverse Events).**
- **Treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds that require additional treatment and prolonged recovery times (see Warnings, Precautions and Adverse Events).**

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

DESCRIPTION
The active ingredient for tigilanol tiglate injection is a phorbol ester that activates alpha, beta I, beta II, and gamma isoforms of protein kinase C. The chemical name is (4S,5S,6R,7S,8R,9R, 10S,11R,12R,13S,14R)-12-(2E)-2-methylbut-2-enoatyl-13-[(2S)-2-methylbutyroyl]-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one. The molecular formula is $C_{30}H_{42}O_{10}$ and its molecular weight is 562.65 g mol^{-1}. Each mL of STELFONTA contains 1 mg tigilanol tiglate and sterile water for injection (60% v/v), propylene glycol (40% v/v), sodium acetate (<0.1% w/v), and glacial acetic acid (<0.1% w/v).

Tigilanol tiglate chemical structure



INDICATION
STELFONTA® injection is indicated for use in dogs for the treatment of:
- non-metastatic cutaneous mast cell tumors
- non-metastatic subcutaneous mast cell tumors located at or distal to the elbow or the hock

DOSAGE AND ADMINISTRATION
ALWAYS PROVIDE THE CLIENT INFORMATION SHEET TO THE DOG OWNER BEFORE DOSE ADMINISTRATION. Carefully consider the potential benefits and risks of STELFONTA before deciding to use STELFONTA.

It is crucial to follow the dosing and administration instructions to use the product safely and effectively (see **Boxed Warning, Animal Warnings, Precautions, Clinical Pharmacology**).

Concomitant medications
Administer the following medications to decrease the potential for severe systemic adverse reactions from mast cell degranulation (see **Effectiveness**). Do not underdose concomitant medications and confirm that the dog owner administered the medications as prescribed prior to the day of STELFONTA treatment.
- **Corticosteroid (oral prednisone or prednisolone at anti-inflammatory dose):** Start medication 2 days prior to STELFONTA treatment at a dose of 0.5 mg/kg orally every 12 hours for 7 days (2 days prior, the day of treatment, and 4 days after treatment), then 0.5 mg/kg orally every 24 hours for an additional 3 days (10 days total).
- **H1 receptor blocking agent (oral diphenhydramine):** Start medication on the day of STELFONTA treatment at a dose of 2 mg/kg orally every 12 hours and continue for a total of 8 days (the day of treatment and 7 days after treatment).
- **H2 receptor blocking agent (oral famotidine):** Start medication on the day of STELFONTA treatment at a dose of 0.5 mg/kg orally every 12 hours and continue for a total of 8 days (the day of treatment and 7 days after treatment).
- Fill out the medication schedule (drug name, dose, route of administration, date) on the Client Information Sheet to help the dog owner administer these medications correctly.

Consider administering analgesic medications prior to, during, and after treatment with STELFONTA.

Dosing Instructions
Administer STELFONTA as an intratumoral injection at a dose of 0.5 mL per cm^3 of tumor volume, as determined by the following calculations:

STEP 1. Calculate Tumor Volume:
- Measure the tumor dimensions (Length, Width and Height) with calipers on the day of STELFONTA injection.
- Determine the Tumor Volume using the modified ellipsoid formula to account for the tumor shape (cube volume x ½) as below:

Modified ellipsoid calculation

_____ X _____ X _____ X ½ = _____ cm^3
Length (cm) Width (cm) Height (cm) Tumor Volume

- Confirm the Tumor Volume does not exceed 10 cm^3.
- Do not use STELFONTA if Tumor Volume is >10 cm^3.

STEP 2. Calculate the mL of STELFONTA to inject:

_____ Tumor Volume (cm^3) X 0.5 Dose (0.5 mL/cm^3) = _____ mL of STELFONTA mLs to be injected

- Confirm the dose of STELFONTA does not exceed 0.25 mL/kg body weight and do not use if the calculated dose exceeds this.
- Do not exceed 5 mL per dog, regardless of tumor volume or body weight.
- The minimum dose of STELFONTA is 0.1 mL, regardless of tumor volume or body weight. If the calculated dose is < 0.1 mL, administer 0.1 mL.
- **Confirm the calculated dose of STELFONTA** using the online dosing calculator at www.stelfonta.com/calculator (or scan the QR code to the right).

Administration of STELFONTA:
Sedation may be necessary to safely and accurately administer STELFONTA to decrease the chance of accidental self-injection. Wear gloves, eye protection, and lab coat or gown in the preparation and administration of STELFONTA. Care should be taken to restrict injections to the tumor only. STELFONTA should not be injected into the margins, beyond the periphery, or deep to the tumor.
- Shave the tumor site. Avoid manipulation of the tumor.
- Draw the calculated volume of STELFONTA into a sterile Luer-lock syringe with a 23 gauge needle.
- Identify an appropriate injection point on the edge of the tumor. See Figure 1. Insertion of the needle depends on the tumor's location, form, and appearance. If a tumor protrudes above the surface of the skin, insert the needle at an oblique angle of approximately 45°.
- Insert and embed the needle in the tumor through a single injection site and draw the syringe plunger back slightly to ensure STELFONTA is not injected into a blood vessel. While applying even pressure on the syringe plunger, move the needle back and forth in a fanning manner to inject STELFONTA into the tumor. See Figure 1. The drug should fully perfuse the entire tumor.
- When the total dose of STELFONTA has been administered, pause to allow tissue dispersion before removing the needle from the tumor. Pull back on the syringe plunger to create a small negative pressure before removing the needle to minimize leakage from the injection site.
- After the needle is withdrawn, apply light pressure for 30 seconds over the needle exit hole using a gloved finger. If leakage does occur, rinse injection site with saline to wash STELFONTA from the skin surface. Do not re-administer.
- To minimize risk of accidental self-injection, do not recap the needle. Dispose of the needle and syringe.

Figure 1: Dispersion of STELFONTA throughout the tumor.

CONTRAINDICATIONS
Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see **Adverse Reactions**).

WARNINGS
Human Safety Warnings
NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

Caution is required during treatment to avoid accidental self-injection. Dogs undergoing treatment with STELFONTA should be adequately restrained and sedation used if necessary. Use a Luer-lock syringe to administer STELFONTA. Do not recap the needle. Accidental self-injection may result in local inflammatory reactions, including swelling, redness and severe wound formation. In case of accidental self-injection, immediately rinse the area with water, seek medical advice immediately, and show the package insert to the physician.

Wear personal protective equipment consisting of disposable gloves, protective eye wear, and a lab coat or gown when handling STELFONTA. STELFONTA is an irritant and accidental exposure to skin, eye, or by ingestion should be avoided. In case of dermal or ocular exposure, repeatedly wash the exposed skin or eye with water. If wearing contacts, rinse they eyes first then remove contacts and continue to rinse with water. If symptoms such as local signs of redness and swelling occur, or if there has been ingestion, seek the advice of a physician and show them the package insert.

Limited data is available on the potential teratogenic effects of STELFONTA. Therefore, STELFONTA should not be administered by women who are pregnant or planning to become pregnant.

People with known hypersensitivity to tigilanol tiglate or to any of the excipients should avoid contact with STELFONTA.

Animal Safety Warnings
Dogs should be monitored during and for 5-7 days after intratumoral treatment with STELFONTA for signs of systemic mast cell degranulation such as vomiting, diarrhea, lethargy, anorexia/hyporexia, altered breathing, hypotension, urticaria, edema at or away from the treated site, or bruising at or away from the treated site. If signs are observed, appropriate treatment should be started immediately.

Always administer the concomitant medications (prednisone or prednisolone, diphenhydramine, and famotidine), as directed in the Dosage and Administration section, with STELFONTA in order to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation (see **Adverse Reactions**).

Treatment with STELFONTA causes tumor necrosis which is part of the mechanism of action of the drug. Bruising, heat, pain, and swelling may begin at the site within 2 hours of treatment. By day 7 after treatment, wound formation including full thickness dermal necrosis with exudate, peripheral tissue edema, erythema, skin discoloration, tissue sloughing, and necrotic eschar may occur.

STELFONTA can induce a substantial local inflammatory reaction which may result in severe pain and swelling, bruising, cellulitis, extensive wound formation, and severe tissue sloughing extending away from the treated site. Consider administering analgesic medications prior to, during, and after treatment with STELFONTA in addition to the use of corticosteroids and both H1 and H2 receptor blocking agents.

Amputation of an extremity has been reported in some cases (see **Post-Approval Experience**).

Some dogs require wound care and pain management for an extended period.

Do not inject STELFONTA into normal subcutaneous tissue or adjacent tissues (e.g., beyond tumor margins) because severe edema, erythema, and necrosis of the injected tissue may occur.

PRECAUTIONS
STELFONTA is not intended for the treatment of metastatic mast cell tumors.

The safe and effective use of STELFONTA has not been evaluated in dogs with a mast cell tumor volume >10 cm^3.

Use STELFONTA with caution in tumors located within mucocutaneous regions (e.g., eyelids, vulva, prepuce, and anus) as tumor necrosis could cause a change in morphology of the mucocutaneous region resulting in loss of functional integrity.

Use STELFONTA with caution in mast cell tumors with significant ulceration as leakage of the drug from the ulcerated area may occur following treatment potentially reducing effectiveness.

Some discharge from the site following treatment is expected. Wear disposable gloves to clean the site with warm water as necessary.

After treatment with STELFONTA, dogs may require additional care of the treated site to aid in the healing process, especially if there is extensive wound formation (see **Animal Safety Warnings** and **Post-Approval Experience**).

Tongue lesions have been reported (see **Post-Approval Experience**). Do not allow the dog to lick the site for the first few days after treatment. Discourage excessive licking for the remainder of the healing period.

An Elizabethan collar or a non-constricting dry gauze bandage may be needed to prevent the dog from self-traumatizing the treated site.

After treatment with STELFONTA, separation from other household animals may be necessary to prevent grooming and trauma to the treated site.

STELFONTA has not been evaluated in dogs with signs of systemic disease due to the mast cell tumor(s).

The safe and effective use of STELFONTA has not been evaluated for simultaneous treatment of more than one mast cell tumor.

The safe use of STELFONTA has not been evaluated in dogs with concurrent diseases that may result in delayed wound healing.

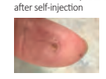
The safe use of STELFONTA under conditions of use has not been evaluated in dogs younger than 3.5 years old.

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

ADVERSE REACTIONS
Human Exposure
There was one human exposure during the field study where the veterinarian had a needle stick injury to the thumb at completion of tumor treatment and was injected with an unknown amount of STELFONTA. The incident resulted in pain and necrosis of the center of the thumb at the point of needle stick. The wound healed over a period of three months. See Pictures 1 and 2 below. A separate needle stick injury was reported with a maximum potential dose of 0.1 mL tigilanol tiglate into the distal extremity of the left index finger, resulting in a localized burning sensation, local inflammation, bruising, muscular pain up the left arm, and localized tissue necrosis. Muscular pain resolved in the first 12-24 hours and the wound healed in 8 weeks. There have been other needle stick injuries reported, with at least one injection into a thumb, with minimal (stinging, pain, and swelling) to no adverse events associated with these accidental self-injections.

Picture 1. Thirteen days after self-injection

Picture 2. Seventy-four days after self-injection



(CONTINUED ON NEXT PAGE)

PRODUCT INSERTS/DISCLOSURES

(CONTINUED FROM PREVIOUS PAGE)

Field Study

In a well-controlled, multi-center, randomized, double-masked field study evaluating the effectiveness and safety of STELFONTA for the treatment of cutaneous and subcutaneous mast cell tumors in dogs, 117 dogs treated with STELFONTA and 42 dogs receiving sham treatment (untreated control) were evaluated for safety. Eighty-one dogs were treated with STELFONTA on Day 0. Thirty-six previously untreated control dogs were treated with STELFONTA on Day 30. In addition, 18 dogs treated with STELFONTA on Day 0 had the same tumor re-treated with STELFONTA on Day 30 due to incomplete response. The most common adverse reactions included wound formation, injection site pain, lameness in the treated limb, vomiting, diarrhea, and hypoalbuminemia. Wound formation, vomiting, and diarrhea were mainly observed within the first 7 to 10 days after treatment. Injection site pain and lameness in the treated leg were mainly observed within the first 2 days after treatment. Hypoalbuminemia was mainly observed within the first 28 days after treatment. All dogs received concomitant medications as noted in the Effectiveness section. The adverse reactions during the study are summarized in Table 1 below.

Table 1: Adverse Reactions During the Field Study

Adverse Reaction	STELFONTA 1st Treatment (n = 117)	STELFONTA 2nd Treatment (n = 18)	UNTREATED CONTROL (n = 42)
Wound formation	110 (94.0%)	12 (66.7%)	3 (7.1%)
Injection site pain	61 (52.1%)	7 (38.9%)	1 (2.4%)
Lameness in treated limb	29 (24.8%)	2 (11.1%)	1 (2.4%)
Vomiting	24 (20.5%)	3 (16.7%)	4 (9.5%)
Diarrhea	24 (20.5%)	3 (16.7%)	2 (4.8%)
Hypoalbuminemia[a]	21 (18.0%)	2 (11.1%)	1 (2.4%)
Injection site bruising/ erythema/edema/irritation	20 (17.1%)	3 (16.7%)	1 (2.4%)
Anorexia	14 (12.0%)	2 (11.1%)	3 (7.1%)
Regional lymph node swelling/enlargement	13 (11.1%)	1 (5.6%)	1 (2.4%)
Tachycardia	12 (10.3%)	0 (0.0%)	1 (2.4%)
Weight loss	12 (10.3%)	3 (16.7%)	5 (11.9%)
Cystitis	10 (8.6%)	1 (5.6%)	2 (4.8%)
Dermatitis	9 (7.7%)	1 (5.6%)	1 (2.4%)
Personality/behavior change	8 (6.8%)	0 (0.0%)	2 (4.8%)
Infection at injection site	8 (6.8%)	0 (0.0%)	0 (0.0%)
Tachypnea	7 (6.0%)	2 (11.1%)	1 (2.4%)
Pruritus	6 (5.1%)	3 (16.7%)	2 (4.8%)
Lethargy/Depression	6 (5.1%)	1 (5.6%)	1 (2.4%)
Pyrexia	3 (2.6%)	2 (11.1%)	0 (0.0%)

[a] There was a statistically significant decrease in albumin and albumin/globulin ratios at Day 7 in the STELFONTA group compared to the control group. The hypoalbuminemia ranged from 2.0 to 2.6 g/dL (reference range 2.7-3.9 g/dL). Note: If an animal experienced the same adverse reaction more than once, only the highest grade was tabulated.

Adverse reactions were graded using the Veterinary Co-operative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE).[1] Most adverse reactions were Grade 1 (mild) or 2 (moderate). Grade 3 (severe) and 4 (life-threatening) adverse reactions in dogs treated with STELFONTA included: lameness in the treated limb (6 dogs), injection site pain (4 dogs), wound formation (3 dogs), lethargy/ depression (3 dogs), anorexia (2 dogs), infection at injection site (1 dog), pruritis (1 dog), and tachycardia (1 dog).

Adverse reactions associated with use of the required concomitant corticosteroids were similarly reported in STELFONTA and untreated control dogs and included elevated alkaline phosphatase, polyuria, and polydipsia.

Wound Formation

Tumor observations were conducted at 2, 4, 8, and 24 hours and 4 days after treatment. The 81 dogs treated with STELFONTA on Day 0 were reported most frequently with swelling, bruising, pain and heat at all tumor observation timepoints. The following were reported at 24 hours post treatment:

- Swelling: 97.5% (79/81 dogs)
- Pain: 69.1% (56/81 dogs)
- Bruising: 91.4% (74/81 dogs)
- Heat: 53.1% (43/81 dogs)

At 24 hours post treatment, intact skin was reported in 71.6% (58/81 dogs) of STELFONTA treated dogs. On Day 4 intact skin was reported in 17.3% (14/81 dogs) of STELFONTA treated dogs. On Day 4, the following observations were reported with the highest frequency:

- Necrosis: 55.6% (45/81 dogs)
- Crater pockets: 37.0% (30/81 dogs)
- Exudate: 37.0% (30/81 dogs)
- Eschar: 28.4% (23/81 dogs)
- Ulceration: 11.1% (9/81 dogs)

A wound healing assessment was performed on the effectiveness dataset which included 80 dogs in the STELFONTA group and 38 dogs in the untreated control group. Wounds developed in 92.5% (74/80) of STELFONTA treated dogs and 2.6% (1/38) of untreated control dogs by Day 7. On Day 28, the presence of wounds was 40% (32/80) in the STELFONTA group and 2.6% (1/38) in the untreated control group. On Day 42 and Day 84, the presence of wounds was 27.1% (16/59) and 1.8% (1/57), respectively, in the STELFONTA group.

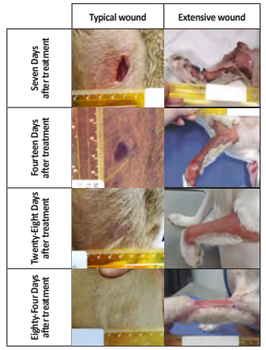
Exudate from the treated site including serous, serosanguinous, sanguineous, seropurulent, and purulent discharges were seen mainly on Day 7 and to a lesser extent on Day 14. Sloughing of the treated site was observed from Day 7 to Day 42, with decreasing frequency after Day 7.

Peripheral pitting or non-pitting edema and erythema of the surrounding area were observed from Day 7 to Day 28, with decreasing intensity and frequency after Day 7. Necrotic eschar and epithelialization of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14. Granulation or hyper-granulation of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14.

The average wound size at Day 7 for a STELFONTA treated dog was 3.3 cm x 2.4 cm (original average tumor size 1.9 x 1.6 x 0.9 cm). On Day 28, the average wound size was 2.0 x 1.4 cm.

The largest total wound for a STELFONTA treated dog was reported seven days after treatment. The treated tumor was located on the left caudal stifle and the original tumor size measured 2.4 x 2.1 x 1.4 cm. The wound area initially consisted of three individual wounds recorded on the treated limb (both medial and lateral sides): 7.5 x 4.5 cm, 7.0 x 3.5 cm, and 11.5 x 7.0 cm. The wounds had reduced to 3.5 x 1.4 cm, 3.9 x 1.5 cm, and 9.7 x 4.3 cm 28 days after treatment, and 0.5 x 0.7 cm and 2.5 x 2.9 cm 42 days after treatment and were no longer present at 84 days after treatment.

One dog treated with STELFONTA was reported with an extensive wound formation (wound size 25.0 x 9.5 cm) with severe tissue slough (Grade 3) nine days after treatment of a mast cell tumor on the left metacarpal area (original tumor size 2.5 x 1.9 x 1.3 cm). The wound extended proximally up the leg to the shoulder and required bandaging of the leg and antibiotics. Scar contracture formed, requiring treatment under sedation to release the scar tissue. Clinical pathology abnormalities included elevated band neutrophils, anemia, and hypoalbuminemia. The wound had not fully healed by the end of the study 89 days after treatment. See pictures below comparing progression of this extensive wound formation versus commonly observed wound progression.



One dog treated with STELFONTA was reported with a bacterial infection and cellulitis in the right rear leg 9 days after treatment of a mast cell tumor on the right rear paw. There was bruising of the upper thigh and necrotic skin on the caudal right thigh and cranial aspect of the hock. Bloody discharge under the necrotic tissue revealed rod bacteria and toxic neutrophils. The dog was treated with intravenous fluids and antibiotics.

Systemic Mast Cell Degranulation and Death

Two dogs from two separate pilot studies died from a suspected mast cell degranulation reaction. Both dogs were treated with STELFONTA for a subcutaneous mast cell tumor located above the hock and did not receive the concomitant medications as prescribed.

In a pilot field study, one dog with a large (10 cm^3) subcutaneous mast cell tumor on the right hip was treated with STELFONTA. The dog had a partial Response Evaluation Criteria in Solid Tumors Guideline (RECIST)[2] response to the initial STELFONTA injection and was re-treated with STELFONTA, 30 days following the initial injection. The patient did not receive any of the recommended concomitant medications of prednisolone, chlorpheniramine and famotidine from 24 hours after the second STELFONTA injection. On Day 2 following the second STELFONTA injection, the dog became anorexic, painful, and lethargic and had marked swelling of the right hind limb extending to the chest with hemorrhagic, ruptured blisters near the hock joint. Blood work showed anemia, hypoproteinemia, liver enzyme elevations, and white blood cell changes (leukocytosis, neutrophilia, monocytosis, and thrombocytopenia). The dog was hospitalized, received a blood transfusion, and was administered intravenous fluids, prednisolone, chlorpheniramine and tramadol. Pitting edema progressed to the neck by four days following treatment. Despite supportive care, the dog died five days following treatment likely due to degranulation of the mast cell tumor and internal necrotic discharge of the tumor.

In a separate pilot field study, one dog with a moderate (2.53 cm^3) subcutaneous mast cell tumor on the left caudal hindlimb was treated with STELFONTA. The dog was treated with chlorpheniramine and meloxicam on the treatment day (Day 0) and Day 1 only. The dog did not receive further concomitant medication. On Day 3 the dog was lethargic and there was significant edema at the injection site. While intravenous fluid and antibiotic therapy was initiated on Day 3, the dog rapidly deteriorated and died on the following day likely due to degranulation of the mast cell tumor. Pathology findings included widespread cellulitis, panniculitis (likely of bacterial origin), and septic peritonitis.

Post-Approval Experience (2024)

The following adverse events are based on post-approval adverse drug experience reporting for STELFONTA. 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 following adverse events reported in dogs are listed in decreasing order of reporting frequency:

Injection site reactions (wound formation, swelling, pain, necrosis, skin sloughing, bleeding, bruising and erythema). These injection site reactions varied in severity and ranged from localized to extending away from the injection site.

Other signs reported include anorexia, lameness, lethargy, diarrhea, vomiting, fever, tachypnea/dyspnea, and ulceration or necrosis of tongue.

In some cases, when STELFONTA was used to treat a mast cell tumor on an extremity, the entire extremity became swollen, painful, and developed tissue sloughing. Some of these cases resulted in amputation.

In some cases, death (including euthanasia) has been reported as an outcome of the adverse events reported above.

CONTACT INFORMATION

To report suspected adverse drug experiences, to obtain a Safety Data Sheet (SDS), or for technical assistance, contact Virbac at 1-800-338-3659 or us.virbac.com.

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

INFORMATION FOR DOG OWNERS

Owners should be given the Client Information Sheet (CIS) to read before STELFONTA is administered.

Owners should be advised to observe their dog for potential side effects, including signs of systemic mast cell degranulation, excessive pain and swelling, and excessive wound formation. Advise dog owners about the possibility of severe side effects, including amputation and death, when to contact a veterinarian, and how to care for the treated tumor site.

Some discharge from the site following treatment is expected. The site can be cleaned with warm water as necessary. Advise owners to wear disposable gloves when cleaning the area.

Discuss the importance of the concomitant medications and ensure that the owner is aware of the schedule of medications that should be administered. The owner should use the Medication Schedule on the CIS to keep track of the medications they have administered.

Discuss with owners that they should not allow the dog to lick the site for the first few days after treatment and they should discourage excessive licking for the remainder of the healing period.

An Elizabethan Collar may be utilized to prevent self-trauma of the treatment site. After treatment the owner may need to separate the dog from other household animals to prevent grooming and trauma to the treated site.

CLINICAL PHARMACOLOGY

Mechanism of Action

In non-clinical pharmacology studies, tigilanol tiglate has been shown to have three inter-related effects that are responsible for its anti-tumor effectiveness. The first effect is to cause oncolysis of tumor cells that are in direct contact with tigilanol tiglate. The oncolysis occurs within the first hours following treatment and results from the disruption of mitochondrial functioning. Secondly, at the same time, tigilanol tiglate activates a protein kinase C (PKC) signaling cascade which propagates throughout the tumor, resulting in an acute inflammatory response with swelling and erythema extending to the tumor margins and immediate surroundings. This inflammatory response is normal and necessarily contributes to the activity of tigilanol tiglate by (a) restricting blood and oxygen supply to the tumor (causing localized hypoxia) and (b) recruiting and activating innate immune cells (principally neutrophils and macrophages), which then target the tumor and release reactive oxygen species, proteases, and cytokines that function in an antimicrobial role. This acute inflammatory response generally resolves within 48 to 96 hours. The third component of the antitumor activity of tigilanol tiglate is associated with direct effects of the drug in increased permeability of the tumor vasculature (via activation of the Beta-II isoform of PKC) leading to tumor vascular destruction. The resulting outcome is tumor destruction with a deficit or wound remaining where the tumor was located. Complete healing of the resulting wound following tumor destruction by STELFONTA is typically within 6 weeks.

Pharmacokinetics

Pharmacokinetic properties of STELFONTA were evaluated in a pilot study monitoring systemic levels following intratumoral injection, with a dose delivered according to the size of the mast cell tumor. A dose of 0.5 mg/cm^3 (0.5 mL/cm^3) was used in dogs with tumor volumes ranging from 0.1 to 6.8 cm^3 resulting in doses ranging from 0.002 mg/kg to 0.145 mg/kg and total doses ranging from 0.05 mg to 3.4 mg per dog. A total of 6 cutaneous and 5 subcutaneous mast cell tumors were treated in 10 dogs (one dog had two tumors treated consecutively). The following range of pharmacokinetic parameters were determined for STELFONTA in plasma: 1) elimination half-life ($t_{½}$): 2.85 to 36.87 hours; 2) maximum plasma concentration (C_{max}): 0.356 ng/mL to 13.8 ng/mL; and 3) area under the plasma concentration time-curve to the last quantifiable plasma concentration (AUC_{last}): 2.25 h*ng/mL to 31.24 h*ng/mL. There was no relationship between drug exposure (C_{max} and AUC_{last}) with tumor location (cutaneous or subcutaneous) or with total dose. In an evaluation of the pharmacokinetic data from the 5 dogs with cutaneous tumors, dose levels ranged from 0.002 mg/kg to 0.145 mg/kg. The highest C_{max} was 11.1 ng/mL and the highest AUC_{last} was 31.24 h*ng/mL at a dose of 0.125 mg/kg. For the other 5 dogs with subcutaneous tumors, doses ranged from 0.049 mg/kg to 0.094 mg/kg. The highest C_{max} was 13.8 ng/mL and the highest AUC_{last} was 30.81 h*ng/mL at a dose of 0.094 mg/kg.

(CONTINUED ON NEXT PAGE)

(CONTINUED FROM PREVIOUS PAGE)

EFFECTIVENESS

The effectiveness of STELFONTA was evaluated in a well-controlled, multi-center, randomized, double-masked, field study in client-owned dogs. Enrolled dogs had non-metastatic World Health Organization stages Ia (one tumor confined to the dermis, without regional lymph node involvement) and IIIa (multiple dermal tumors; large infiltrating tumors without regional lymph node involvement) mast cell tumors that were (i) cutaneous, or (ii) subcutaneous and located at or distal to the elbow or the hock. A total of 123 client-owned dogs with a mast cell tumor measuring less than or equal to 10 cm^3 were randomized to treatment with a single injection of STELFONTA (n=81) or untreated control (n=42). On the day of treatment, the average tumor volume was 1.7 cm^3 (range 0.1 to 9.8 cm^3).

A total of 118 dogs were included in the effectiveness analysis; 80 dogs were in the STELFONTA group and 38 dogs were in the untreated control group. Response to treatment was evaluated using the RECIST[2], where complete response (CR) is resolution of the target tumor, partial response (PR) is at least a 30% decrease in the longest diameter of target tumor, stable disease (SD) is a decrease of less than 30% or increase of less than 20% of the longest diameter of the target tumor, and progressive disease (PD) is greater than a 20% increase in the longest diameter of the target tumor.

The primary effectiveness variable compared CR rates of the target tumor between groups 28 days after treatment. At 28 days after treatment, a statistically significantly greater proportion of dogs in the STELFONTA treated group (60/80; 75%) achieved CR compared to dogs in the untreated control group (2/38; 5.3%) (p<0.0001). An objective tumor response (CR + PR) was observed in 64/80 (80%) of the STELFONTA treated dogs. Of the 60 dogs in the STELFONTA group that experienced CR at Day 28, response assessment was conducted for 59 dogs at Day 42 and for 57 dogs at Day 84. At Day 42, 59/59 (100%) were disease-free at the injection site, and at Day 84, 55/57 (96%) were disease-free at the injection site.

For all dogs, corticosteroids (prednisone or prednisolone) were initiated 2 days prior to treatment at a dose of 0.5 mg/kg orally twice daily and continued for 7 days total (2 days before, on the day of treatment and 4 days after treatment), then 0.5 mg/kg once daily for an additional 3 days. An H1 receptor blocking agent (diphenhydramine [2 mg/kg orally twice daily]) and H2 receptor blocking agent (famotidine [0.5 mg/kg orally twice daily]) were initiated on the day of treatment and continued for 7 days.

Other medications prescribed based on veterinary discretion included antibiotics, analgesics, and sedatives. The majority of antibiotics were used to treat injection site infections. The majority of analgesics were used to treat tumor pain and were mainly initiated on the day of or day after treatment. Sedatives were used for treatment administration, conducting diagnostics, anxiety, and temperament issues.

Quality of Life (QoL)[3] was assessed by owners throughout the study and the mean scores for the QoL assessment was similar between the STELFONTA and untreated control groups at all time points.

Eighteen of the 20 STELFONTA treated dogs without CR received a second treatment. Twenty-eight days following the second treatment, CR was observed in 8/18 (44.4%) of these dogs. Forty-two days following the second treatment, CR was observed in 7/18 (38.9%) of treated dogs.

TARGET ANIMAL SAFETY

The margin of safety and toxicity of STELFONTA was evaluated in one laboratory safety study and one laboratory cardiovascular study utilizing final market formulation, and one pilot field study that used non-commercial formulation.

Laboratory Safety Study

In a 4-week laboratory safety study, 48 healthy Beagle dogs 6 to 8 months old were administered STELFONTA intravenously over a 15-minute infusion once a week for four weeks on Days 1, 8, 15, and 22, at doses of 0, 0.025, 0.05, or 0.075 mg/kg body weight (ranges between 0.02-0.036, 0.039-0.056, and 0.06-0.08 mg/kg, respectively due to dosing variability). Control dogs (0 mg/kg) received a vehicle control at a volume equal to the 0.075 mg/kg dose. The intravenous route was chosen for this study because subcutaneous injection was too toxic and intratumoral administration was not possible.

There were twelve dogs per group (6 male, 6 female). Four dogs/sex/group were necropsied two days following the last dose and two dogs/sex/group were necropsied following a 2-week recovery period.

All dogs survived the study, and there were no STELFONTA-related effects on body weight, body temperature, ophthalmic exam, electrocardiographic parameters, and organ weights.

The following were observed only in dogs in the groups administered STELFONTA: decreased food consumption from Days 22-29, vomiting/retching during infusion or immediately post-infusion, wound formation at the infusion site after the second or third dose, decrease in activity sporadically throughout the study, and elevations in alanine aminotransferase on Day 23.

The following were observed in all groups, including vehicle control and increased in a dose dependent manner: limited use of the leg that received the infusion occurred soon after dosing, weakness after the first dose, salivation and infusion site edema and erythema increased in frequency and severity throughout the study, and tremors occurred immediately post-infusion and increased in severity with dose.

Vomiting, retching, or tremors were typically transient and resolved within 1 hour of dosing while salivation also typically resolved within 4 hours.

Loose feces were observed in all groups in a non-dose dependent manner. Polydipsia occurred in the control, 0.05 and 0.075 mg/kg groups. Trending towards decreasing hematocrit (but still within reference intervals) was observed in all groups. One dog in the 0.05 mg/kg group was mildly anemic during recovery. Monocytosis and elevated fibrinogen were seen on Days 2 and 23 in a dose-dependent manner.

Gross pathology findings at the infusion site included inflammation, redness, and thickening of the skin. Correlative histopathology findings of the infusion site included hemorrhage, edema, inflammation, mixed cell infiltration, fibrosis, and chronic organizing thrombosis. Only one of the recovery dogs had changes at the infusion site consisting of proliferation of the intima. One dog in the 0.075 mg/kg group had a severe wound, confirmed on histopathology as ulcerative inflammation and severe necrosis with bacteria present. Gross pathology findings also included red, mottled, firm, and enlarged lymph nodes in all dose groups, including recovery dogs, confirmed on histopathology as inflammation, lymphoid hypercellularity, hemorrhage, and sinus histiocytosis. Pituitary cysts were observed in 7 dogs in all STELFONTA treated groups. One dog each from the 0.075 mg/kg group was observed to have kidney tubular vacuolation, dilation of the ventricles of the brain, and chronic inflammation of both the left thigh skeletal muscle and left sciatic nerve.

Laboratory Cardiovascular Study

In a 12-day laboratory cardiovascular study, 4 healthy male conscious telemeterized Beagle dogs approximately 2-4 years old were administered STELFONTA as a single intravenous infusion. Treatment consisted of four groups: vehicle control and STELFONTA at doses of 0.01, 0.025 and 0.075 mg/kg body weight. All four dogs received all treatments with at least a 3-day wash-out period.

All dogs survived the study and there were no STELFONTA-related effects on body temperatures, blood pressure, or electrocardiograms. The following were observed only after administration of STELFONTA in all dose groups: salivation, vocalization, incoordination, tremors, red feces, and decreased feces output. Retching, vomiting, incoordination, and changes in activity levels (increased and decreased) occurred in the 0.075 mg/kg group only. Tachycardia was seen for the first 2.5 hours after the 0.075 mg/kg dose only. The following were observed after administration of control or STELFONTA: excessive panting, decreased appetite, and limited usage/swelling of leg or paw. All dogs lost weight during the study. Clinical signs resolved around 4 hours post dosing.

Pilot Field Study

In a 28-day unmasked field study, 10 client-owned dogs, 6-14 years old were administered tigilanol tiglate (non-commercial formulation) once as an intratumoral injection at a dose of 0.5 mg tigilanol tiglate per cubic centimeter (cm^3) of tumor volume, not exceeding 0.25 mg/kg body weight (maximum dose of 5 mg). One dog was enrolled a second time to treat a second mast cell tumor after successful treatment of the first tumor. See pharmacokinetic results from this study under **Clinical Pharmacology**.

The most common observations after tigilanol tiglate administration were injection site reactions including necrosis, swelling (localized edema and edema extending well beyond the tumor injection site), pain, restlessness, inflammation, erythema, bleeding ulcerations, bruising/discoloration, sloughing of tissue, open wound, mild drainage, malodor, and presence of granulation tissue. Three dogs experienced dermatitis with or without skin necrosis in a region nearby but distinct from the tumor injection site. One dog experienced non-weight bearing lameness, muscle atrophy and enlarged popliteal lymph node. One dog vomited after administration. Three dogs required longer healing times beyond 28 days, with the longest requiring 5 months. Hypoalbuminemia was observed in 5 dogs with hypoproteinemia observed in 1 of these 5 dogs on Day 7 and was resolved by Day 28.

STORAGE INFORMATION

Store STELFONTA vials refrigerated at 2°C to 8°C (35°F to 46°F).
Do not freeze.
Keep the vial in the carton at all times to protect the vial from light.
For single use only.
Dispose of any unused product in accordance with disposal for routine medical waste.

HOW SUPPLIED

STELFONTA is supplied as a sterile, colorless liquid in a 5 mL clear, single-use glass vial containing 2 mL of STELFONTA at a concentration of 1 mg/mL tigilanol tiglate in sterile water for injection.

REFERENCES

1.Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol*. 20 Jul 2011, DOI: 10.1111/j.1476-5829.2011.00283.x

2. Eisenhauer EA, Therase P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1), *Eur J Cancer.* 2009; 45(2):228-247.

3. Lynch S, Savary-Bataille K, Leeuw B, Argyle DJ. Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer. *Vet Compar Oncol*. 2011; 9 (3):172-82.

Approved by FDA under NADA # 141-541

Distributed by Virbac AH, Inc., P.O. Box 162059, Fort Worth, TX 76161
Tel. 1-800-338-3659 PC5111B
Version date: November 2024 A-IN-001.02

LEGAL STATUS - In order to be legally marketed, a new animal drug intended for a minor species must be Approved, Conditionally Approved, or Indexed by the Food and Drug Administration.
THIS PRODUCT IS INDEXED - MIF # 900-013. Extra-label use is prohibited. FOR USE IN FERRETS ONLY
This product is not to be used in animals intended for use as food for humans or food-producing animals.

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

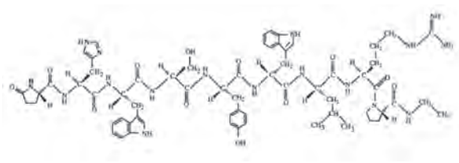
Suprelorin® F

(DESLORELIN ACETATE) 4.7 mg Implant

DESCRIPTION

Suprelorin® F (4.7 mg) Implant is a synthetic GnRH analogue (deslorelin acetate) in a biocompatible, slow release subcutaneous implant. The implant is a solid, opaque, white to pale yellow cylinder, 2.3 mm x 12.5 mm in length and weighing 50 mg. The **Suprelorin® F** (4.7 mg) Implant comes pre-loaded in an implanting needle. Each implant contains 4.7 mg deslorelin (as deslorelin acetate) in an inert matrix.

Chemical Structure – Deslorelin acetate



[(6-D-tryptophan-9-(N-ethyl-L-prolinamide)-10-deglycinamide]GnRH

INDICATIONS

Suprelorin® F (4.7 mg) Implant is indicated for the management of adrenal gland cortical disease in the male and female domestic ferret.

DOSAGE AND ADMINISTRATION

The recommended dosage is one, 4.7 mg implant per ferret every 12 months. Appropriate clinical monitoring is suggested to determine that the symptoms of adrenal disease are being adequately controlled.

Do not use if the foil pouch is damaged.

Remove Luer Lock cap from the implanting needle. Attach the actuator syringe to the implanter using the luer lock connection. One implant should be implanting needle subcutaneously at the dorsal aspect of the base of the neck. Administer only one implant per ferret. Select the implant site by locating the area of the back midway between the shoulder blades. It is not necessary to prepare the implantation site. If the hair is long, a small section may be clipped if required. Lift the loose skin between the shoulder blades. Insert the entire length of the needle subcutaneously. Fully depress the actuator syringe plunger. Press the skin at the insertion site as the needle is slowly withdrawn, and maintain pressure for 30 seconds. Examine the implanting needle to verify that the implant has not remained within the needle, and that the blue plastic spacer is visible at the tip of the needle. It may be possible to palpate the implant *in situ*. The biocompatible implant does not require removal. Wash hands after use.

Repeat treatment every 12 months to maintain efficacy. Appropriate endocrine testing and clinical monitoring should be performed at appropriate intervals to monitor the response to therapy.

CONTRAINDICATIONS

Do not use this product in ferrets with known hypersensitivity to deslorelin acetate or other synthetic hormones.

HUMAN SAFETY WARNINGS

KEEP OUT OF REACH OF CHILDREN. DO NOT HANDLE THIS PRODUCT IF YOU ARE PREGNANT OR NURSING OR SUSPECT YOU MAY BE PREGNANT. Accidental administration may lead to a disruption of the menstrual cycle. Avoid direct skin contact with the implant; if skin contact occurs, wash the affected area immediately with soap and water. The use of gloves is advised. As with all injectable drugs causing profound physiological effects, routine precautions should be employed by practitioners when handling and using Suprelorin® F (4.7 mg) Implant to prevent accidental injection. In case of accidental human injection, a physician should be consulted and the implant should be removed.

PRECAUTION

Do not use in animals intended for breeding. The safe use of this product has not been evaluated in pregnant or lactating ferrets.

ADVERSE REACTIONS

It is possible that treated ferrets will exhibit signs of soreness and swelling at the implantation site which should resolve over one or two weeks. Undesirable histology at the site of implantation has not been reported in other species (canine). Other reported side effects include: weight gain, lethargy and failure to respond to therapy.

To report suspected adverse drug events, please call Virbac at 800-338-3659. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

PHARMACOLOGY

Suprelorin® F (4.7 mg) Implant is a controlled release implant containing the GnRH agonist deslorelin. Deslorelin acetate suppresses the reproductive endocrine system, preventing production of pituitary and gonadal hormones. Deslorelin acetate has not been shown to reduce the size of adrenal tumors and is not considered curative.

DISPOSAL

Each implanting needle (sterile) is a single use device. Used needles should immediately be placed in a designated and appropriately labeled "sharps" container. Each actuator syringe (non-sterile) is a multi-use device and should be saved for future use with the remaining implant(s) in the carton. Unused implants should be disposed of in accordance with local environmental requirements.

STORAGE

Store at temperatures between 2˚ and 8˚ C (36˚ and 46˚ F).
Do not freeze.

HOW SUPPLIED

Five (5) or two (2) implants pre-loaded in implanting needles and individually packaged per carton.

For technical assistance, to request an SDS, or to report suspected adverse drug events, please call Virbac at 1-800-338-3659.

Manufactured for:
Virbac AH, Inc.
P.O. Box 162059
Fort Worth, TX 76161

Product of Australia MIF 900-013

Revision 11/2020
L-2000-F-US-3

PRODUCT INSERTS/DISCLOSURES

Tenotryl™ (enrofloxacin)

100 mg/mL Antimicrobial Injectable Solution

For Subcutaneous Use In Beef Cattle And Non-Lactating Dairy Cattle
For Intramuscular Or Subcutaneous Use In Swine
Not For Use In Female Dairy Cattle 20 Months Of Age Or Older Or In Calves To Be Processed For Veal

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

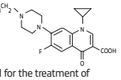
Federal (USA) law prohibits the extra-label use of this drug in food-producing animals.

To assure responsible antimicrobial drug use, enrofloxacin should only be used as a second-line drug for colibacillosis in swine following consideration of other therapeutic options.

PRODUCT DESCRIPTION:
Tenotryl™ is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broad-spectrum fluoroquinolone antimicrobial agent.

Each mL of Tenotryl™ contains 100 mg of enrofloxacin. Excipients are L-arginine base 200 mg, n-butyl alcohol 30 mg, benzyl alcohol (as a preservative) 20 mg and water for injection q.s.

CHEMICAL NOMENCLATURE AND STRUCTURE:
1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid.



INDICATIONS:
Cattle - Single-Dose Therapy: Tenotryl™ is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, *H. somni* and *M. bovis*.

Cattle - Multiple-Day Therapy: Tenotryl™ is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* in beef and non-lactating dairy cattle.

Swine: Tenotryl™ is indicated for the treatment and control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, *Streptococcus suis*, *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*. Tenotryl™ is indicated for the control of colibacillosis in groups or pens of weaned pigs where colibacillosis associated with *Escherichia coli* has been diagnosed.

DOSAGE AND ADMINISTRATION:
Tenotryl™ provides flexible dosages and durations of therapy.

Tenotryl™ may be administered as a single dose for one day for treatment and control of BRD (cattle), for treatment and control of SRD or for control of colibacillosis (swine), or for multiple days for BRD treatment (cattle). Selection of the appropriate dose and duration of therapy for BRD treatment in cattle should be based on an assessment of the severity of the disease, pathogen susceptibility and clinical response.

Cattle:
Single-Dose Therapy (BRD Treatment): Administer, by subcutaneous injection, a single dose of 7.5-12.5 mg/kg of body weight (3.4-5.7 mL/100 lb).

Multiple-Day Therapy (BRD Treatment): Administer daily, a subcutaneous dose of 2.5-5 mg/kg of body weight (1.1-2.3 mL/100 lb).

Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.

Single-Dose Therapy (BRD Control): Administer, by subcutaneous injection, a single dose of 7.5 mg/kg of body weight (3.4 mL/100 lb).

Examples of conditions that may contribute to calves being at high risk of developing BRD include, but are not limited to, the following:

- Transportation with animals from two or more farm origins.
- An extended transport time with few to no rest stops.
- An environmental temperature change of ≥30°F during transportation.
- A ≥30°F range in temperature fluctuation within a 24-hour period.
- Exposure to wet or cold weather conditions.
- Excessive shrink (more than would be expected with a normal load of cattle).
- Stressful arrival processing procedures (e.g., castration or dehorning).
- Exposure within the prior 72 hours to animals showing clinical signs of BRD.

Administered dose volume should not exceed 20 mL per injection site.

Table 1 – Tenotryl™ Dose and Treatment Schedule for Cattle*

Weight (lb)	Treatment		Control
	Single-Dose Therapy 7.5 - 12.5 mg/kg Dose Volume (mL)	Multiple-Day Therapy 2.5 - 5.0 mg/kg Dose Volume (mL)	Single-Dose Therapy 7.5 mg/kg Dose Volume (mL)
100	3.5 - 5.5	1.5 - 2.0	3.5
200	7.0 - 11.0	2.5 - 4.5	7.0
300	10.5 - 17.0	3.5 - 6.5	10.5
400	14.0 - 22.5	4.5 - 9.0	14.0
500	17.0 - 28.5	5.5 - 11.5	17.0
600	20.5 - 34.0	7.0 - 13.5	20.5
700	24.0 - 39.5	8.0 - 16.0	24.0
800	27.5 - 45.5	9.0 - 18.0	27.5
900	31.0 - 51.0	10.0 - 20.5	31.0
1000	34.0 - 57.0	11.0 - 23.0	34.0
1100	37.5 - 62.5	12.5 - 25.0	37.5

*Dose volumes have been rounded to the nearest 0.5 mL within the dose range.

Swine:
Administer, either by intramuscular or subcutaneous (behind the ear) injection, a single dose of 7.5 mg/kg of body weight (3.4 mL/100 lb). Administered dose volume should not exceed 5 mL per injection site. For the control of colibacillosis, administration should be initiated within the first 60 days post-weaning when clinical signs are present in at least 2% of the animals in the group. If no improvement is noted within 48 hours, the diagnosis should be reevaluated.

Table 2 – Tenotryl™ Dose Schedule for Swine

Weight (lb)	Dose Volume (mL)
15	0.5
30	1.0
50	1.7
100	3.4
150	5.1
200	6.8
250	8.5

Dilution of Tenotryl: Tenotryl™ may be diluted with sterile water prior to injection. The diluted product should be used within 24 hours. Store diluted solution in amber glass bottles between 5°C - 40°C (41°F – 104°F), excursions are not permitted.

Table 3 – Dilution Schedule*

Swine Weight	mL of Tenotryl™	mL of sterile water	Number of doses
10 lb	34 mL	66 mL	100
15 lb	51 mL	49 mL	100
20 lb	68 mL	32 mL	100
25 lb	85 mL	15 mL	100

*For 1 mL dose volume from diluted solution

Use within 30 days of first puncture and puncture a maximum of 30 times with a 16-gauge needle or smaller, or 4 times with a draw-off spike 4.75 mm or smaller. Any product remaining beyond these parameters should be discarded.

RESIDUE WARNINGS:
Cattle: Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. This product is not approved for female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

Swine: Animals intended for human consumption must not be slaughtered within 5 days of receiving a single-injection dose.

HUMAN WARNINGS:
Not for use in humans. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

PRECAUTIONS:
The effects of enrofloxacin on cattle or swine reproductive performance, pregnancy and lactation have not been adequately determined. The long-term effects on articular joint cartilage have not been determined in pigs above market weight.

Subcutaneous injection in cattle and swine, or intramuscular injection in swine, can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

Enrofloxacin injectable solution contains different excipients than other enrofloxacin products. The safety and efficacy of this formulation in species other than cattle and swine have not been determined.

Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures. Quinolone-class drugs have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. See Animal Safety section for additional information.

ADVERSE REACTIONS:
No adverse reactions were observed during clinical trials.

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

MICROBIOLOGY:
Enrofloxacin is bactericidal and exerts its antibacterial effect by inhibiting bacterial DNA gyrase (a type II topoisomerase) thereby preventing DNA supercoiling and replication which leads to cell death.[1] Enrofloxacin is active against Gram-negative and Gram-positive bacteria.

EFFECTIVENESS:
Cattle: A total of 845 calves with naturally-occurring BRD were treated with enrofloxacin in eight field trials located in five cattle-feeding states. Response to treatment was compared to non-treated controls. Single-dose and multiple-day therapy regimens were evaluated. BRD and mortality were significantly reduced in enrofloxacin-treated calves. No adverse reactions were reported in treated animals.

The effectiveness of enrofloxacin for the control of respiratory disease in cattle at high risk of developing BRD was evaluated in a six-location study in the U.S. and Canada. A total of 1,150 crossbred beef calves at high risk of developing BRD were enrolled in the study. Enrofloxacin (7.5 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within two days after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for success on Day 14 post-treatment. Treatment success in the enrofloxacin group (497/573, 87.83%) was significantly higher ($P = 0.0013$) than success in the saline control group (455/571, 80.92%). In addition, there were more treatment successes (n = 13) than failures (n = 3) in the group of animals positive for *M. bovis* on Day 0 that were treated with enrofloxacin. No product-related adverse reactions were reported.

Swine: A total of 590 pigs were treated with enrofloxacin or saline in two separate natural infection SRD field trials. For the treatment of SRD, the success rate of enrofloxacin-treated pigs that were defined as "sick and febrile" (increased respiratory rate, labored or dyspneic breathing, depressed attitude and a rectal temperature ≥ 104°F) was statistically significantly greater than the success rate of saline-treated "sick and febrile" pigs. For the control of SRD, mean rectal temperature, mortality (one trial) and morbidity were statistically significantly lower for enrofloxacin-treated pigs in pens containing a percentage of "sick and febrile" pigs compared to saline-treated pigs.

The effectiveness of enrofloxacin administered as a single SC dose of 7.5 mg/kg BW for the treatment and control of SRD associated with *M. hyopneumoniae* was demonstrated using an induced infection model study and three single-site natural infection field studies. In the model study, 72 healthy pigs were challenged with a representative *M. hyopneumoniae* isolate and treated with enrofloxacin or saline. A statistically significant ($P < 0.0001$) decrease in the mean total lung lesion score was observed in the enrofloxacin-treated group (4%) compared with the saline-treated group (27%) at 10 days post-treatment. In two field studies evaluating effectiveness for treatment of SRD, a total of 300 pigs with clinical signs of SRD (moderate depression, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) were enrolled and treated with enrofloxacin or saline. At 7 days post-treatment, the cure rate was statistically significantly higher in the enrofloxacin-treated groups (61.3% and 92%) compared with the saline-treated groups (26.7% and 33.3%). In one field study evaluating effectiveness for control of SRD, a group of 400 pigs in which > 15% had clinical signs of SRD (moderate depression score, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) was enrolled and treated with enrofloxacin or saline. At 7 days post-treatment, the cure rate was statistically significantly higher ($P < 0.0002$) in the enrofloxacin-treated group (70.0%) compared with the saline-treated group (48.5%). In addition to *M. hyopneumoniae*, *B. bronchiseptica* was also isolated in sufficient numbers from these field studies to be included in the SRD treatment and control indications.

The effectiveness of enrofloxacin for the control of colibacillosis associated with *E. coli* was evaluated in a multi-site natural infection field study. At each site, when at least 5% of the pigs were defined as "clinically affected" (presence of diarrhea and either depression or gauntness), all pigs were administered enrofloxacin as a single IM dose of 7.5 mg/kg BW or an equivalent dose volume of saline. At 7 days post-treatment, the success rate was statistically significantly higher ($P = 0.0350$) in the enrofloxacin-treated group (61.5%) compared with the saline-treated group (44.7%).

The effectiveness of enrofloxacin administered as a single IM dose of 7.5 mg/kg BW for the treatment and control of SRD or as a single SC dose of 7.5 mg/kg BW for the control of colibacillosis was confirmed by demonstrating comparable serum enrofloxacin concentrations following IM or SC injection into the neck of healthy male and female pigs.

TOXICOLOGY:
The oral LD50 for laboratory rats was greater than 5000 mg/kg of body weight. Ninety-day feeding studies in dogs and rats revealed no observable adverse effects at treatment rates of 3 and 40 mg/kg respectively. Chronic studies in rats and mice revealed no observable adverse effects at 5.3 and 323 mg/kg respectively. There was no evidence of carcinogenic effect in laboratory animal models. A two-generation rat reproduction study revealed no effect with 10 mg/kg treatments. No teratogenic effects were observed in rabbits at doses of 25 mg/kg or in rats at 50 mg/kg.

ANIMAL SAFETY:
Cattle: Safety studies were conducted in feeder calves using single doses of 5, 15 and 25 mg/kg for 15 consecutive days and 50 mg/kg for 5 consecutive days. No clinical signs of toxicity were observed when a dose of 5 mg/kg was administered for 15 days. Clinical signs of depression, incoordination and muscle fasciculation were observed in calves when doses of 15 or 25 mg/kg were administered for 10 to 15 days. Clinical signs of depression, inappetance and incoordination were observed when a dose of 50 mg/kg was administered for 3 days. No drug-related abnormalities in clinical pathology parameters were identified. No articular cartilage lesions were observed after examination of stifle joints from animals administered 25 mg/kg for 15 days.

A safety study was conducted in 23-day-old calves using doses of 5, 15 and 25 mg/kg for 15 consecutive days. No clinical signs of toxicity or changes in clinical pathology parameters were observed. No articular cartilage lesions were observed in the stifle joints at any dose level at 2 days and 9 days following 15 days of drug administration.

An injection site study conducted in feeder calves demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue and underlying muscle. No painful responses to administration were observed.

Swine: Subcutaneous Safety: A safety study was conducted in 32 pigs weighing approximately 57 kg (125 lb) using single doses of 5, 15 or 25 mg/kg daily for 15 consecutive days. Incidental lameness of short duration was observed in all groups, including the saline-treated controls. Musculoskeletal stiffness was observed following the 15 and 25 mg/kg treatments with clinical signs appearing during the second week of treatment. Clinical signs of lameness improved after treatment ceased and most animals were clinically normal at necropsy.

A second study was conducted in two pigs weighing approximately 23 kg (50 lb), treated with 50 mg/kg for 5 consecutive days. There were no clinical signs of toxicity or pathological changes.

An injection site study conducted in pigs demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue. No painful responses to administration were observed.

Intramuscular Safety: A safety study was conducted in 48 weaned, 20- to 22-day-old pigs. Pigs were administered enrofloxacin, at 7.5, 22.5 and 37.5 mg/kg BW by IM injection into the neck once weekly for 3 consecutive weeks. All pigs remained clinically normal throughout the study. Transient decreases in feed and water consumption were observed after each treatment. Mild, transient, post-treatment injection site swellings were observed in pigs receiving the 37.5 mg/kg BW dose.

Injection site inflammation was found on post-mortem examination in all enrofloxacin-treated groups.

STORAGE CONDITIONS: Protect from direct sunlight. Do not refrigerate or freeze. Store at 20-30°C (68-86°F), excursions permitted between 15°C (59°F) to 40°C (104°F). Precipitation may occur due to cold temperature. To redissolve, warm and then shake the vial.

HOW SUPPLIED:
Tenotryl™ (enrofloxacin) Injectable Solution:
100 mg/mL 100 mL Bottle
100 mg/mL 250 mL Bottle
100 mg/mL 500 mL Bottle

REFERENCES:
1. Hooper, D. C., Wolfson, J. S., Quinolone Antimicrobial Agents, 2nd ed, 59 - 75, 1993.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, call 1-800-338-3659.

Virbac AH, Inc.
PO Box 162059
Fort Worth, TX 76161

Rev. 12/21 - 8840520 and 8840530
Approved by FDA under ANADA # 200-688

PRODUCT INSERTS/DISCLOSURES

Virbac

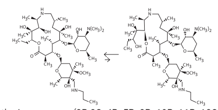
Tulissin®-100-

(tulathromycin injection)
Injectable Solution

Antibiotic
100 mg of tulathromycin/mL
For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves), veal calves, and swine.
Not for use in female dairy cattle 20 months of age or older.

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

DESCRIPTION
TULISSIN 100 Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of TULISSIN 100 contains 100 mg of tulathromycin, 500 mg propylene glycol, 19.2 mg citric acid and 5 mg monothioglycerol. Sodium hydroxide or hydrochloric acid may be added to adjust pH. TULISSIN 100 consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio. Structures of the isomers are shown below.
Figure 1.



The chemical names of the isomers are (2R,3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13 [[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl]-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10-trihydroxy-3, 5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R, 3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl] oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Beef and Non-Lactating Dairy Cattle
BRD - TULISSIN 100 Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*; and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*.

IBK - TULISSIN 100 Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.

Foot Rot - TULISSIN 100 Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.

Suckling Calves, Dairy Calves, and Veal Calves
BRD - TULISSIN 100 Injectable Solution is indicated for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*.

Swine
TULISSIN 100 Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, and *Mycoplasma hyopneumoniae*; and for the control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.

DOSAGE AND ADMINISTRATION

Cattle
Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site.

Table 1. TULISSIN 100 Injectable Solution Cattle Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
100	1.1
200	2.3
300	3.4
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

Swine
Inject intramuscularly as a single dose in the neck at a dosage of 2.5 mg/kg (0.25 mL/22 lb) BW. Do not inject more than 2.5 mL per injection site.

Table 2. TULISSIN 100 Injectable Solution Swine Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
15	0.2
30	0.3
50	0.6
70	0.8
90	1.0
110	1.3
130	1.5
150	1.7
170	1.9
190	2.2
210	2.4
230	2.6
250	2.8
270	3.1
290	3.3

CONTRAINDICATIONS
The use of TULISSIN 100 Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS
FOR USE IN ANIMALS ONLY.
NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS

Cattle
Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows.

Swine
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

PRECAUTIONS

Cattle
The effects of TULISSIN 100 Injectable Solution on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

Swine
The effects of TULISSIN 100 Injectable Solution on porcine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS

Cattle
In one BRD field study, two calves treated with tulathromycin injection at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

Swine
In one field study, one out of 40 pigs treated with tulathromycin injection at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

POST APPROVAL EXPERIENCE
The following adverse events are based on post approval adverse drug experience reporting. Not all adverse events are reported to the 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 following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions.
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
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lungs as compared to the plasma. The extent to which lung concentrations represent free (active) drug was not examined. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.
Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration. Of the two variables, concentration and exposure time, drug concentration tends to be the most powerful determinant of the duration of PAE.
Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

[1] *Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis.,* ***27****:28-32.*
[2] *Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J.,* ***16****:438-443.*

Cattle
Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 15 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tulathromycin distributes extensively into body tissues, as evidenced by volume of distribution values of approximately 11 L/kg in healthy ruminating calves.[3] This extensive volume of distribution is largely responsible for the long elimination half-life of this compound [approximately 2.75 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 8.75 days for total lung concentrations (based on data from healthy animals)]. Linear pharmacokinetics are observed with subcutaneous doses ranging from 1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

[3] *Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.*

Swine
Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (T_{max} ~0.25 hour). Subsequently, the drug rapidly distributes into body tissues, achieving a volume of distribution exceeding 15 L/kg. The free drug is rapidly cleared from the systemic circulation ($CL_{systemic}$ = 187 mL/hr/kg). However, it has a long terminal elimination half-life (60 to 90 hours) owing to its extensive volume of distribution. Although pulmonary tulathromycin concentrations are substantially higher than concentrations observed in the plasma, the clinical significance of these findings is undetermined. There are no gender differences in swine tulathromycin pharmacokinetics.

MICROBIOLOGY

Cattle
Tulathromycin has demonstrated *in vitro* activity against *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, four pathogens associated with BRD; against *Moraxella bovis* associated with IBK; and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot.
The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A2). The MICs against foot rot pathogens were also determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 9:1 isomer ratio of this compound.

BRD - The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders, and from lung swabs or lung tissue of saline- treated calves that died. The results are shown in Table 3.

IBK - The MICs of tulathromycin were determined for *Moraxella bovis* isolates obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from pre-treatment conjunctival swabs of calves with clinical signs of IBK enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.

Foot Rot - The MICs of tulathromycin injection were determined for *Fusobacterium necrophorum* and *Porphyromonas levii* obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from pre-treatment interdigital biopsies and swabs of cattle with clinical signs of foot rot enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.

Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD and IBK in the U.S. and from foot rot field studies in the U.S. and Canada.

Indicated Pathogen	Date isolated	No. of isolates	MIC_{50} † (µg/mL)	MIC_{90} † (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	1999	43	0.125	1	≤ 0.063 to > 64
Moraxella bovis	2004	55	0.5	0.5	0.25 to 1
Fusobacterium necrophorum	2007	116	2	64	≤ 0.25 to > 128
Porphyromonas levii	2007	103	8	128	≤ 0.25 to > 128

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
† The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Swine
In vitro activity of tulathromycin has been demonstrated against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, and *Mycoplasma hyopneumoniae*.
The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for *Haemophilus parasuis* were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO_2-enriched atmosphere. All MIC values were determined using the 9:1 isomer ratio of this compound. Isolates obtained in 2000 and 2002 were from lung samples from saline-treated pigs and non-treated sentinel pigs enrolled in Treatment of SRD field studies in the U.S. and Canada. Isolates obtained in 2007 and 2008 were from lung samples from saline-treated and tulathromycin injection-treated pigs enrolled in the Control of SRD field study in the U.S. and Canada. The results are shown in Table 4.

Table 4. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating SRD in the U.S. and Canada.

Indicated Pathogen	Date isolated	No. of isolates	MIC_{50} † (µg/mL)	MIC_{90} † (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	2000-2002 2007-2008	135 88	16 16	32 16	16 to 32 4 to 32
Haemophilus parasuis	2000-2002	31	1	2	0.25 to > 64
Pasteurella multocida	2000-2002 2007-2008	55 40	1 1	2 2	0.5 to > 64 ≤ 0.03 to 2
Bordetella bronchiseptica	2000-2002	42	4	8	2 to 8

* The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
† The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS

Cattle
BRD – In a multi-location field study, 314 calves with naturally occurring BRD were treated with tulathromycin injection. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. The cure rate was significantly higher (P ≤ 0.05) in tulathromycin injection-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the tulathromycin injection-treated calves compared to nine BRD-related deaths in the saline-treated calves.
Fifty-two tulathromycin injection-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs.
Of the 52 tulathromycin injection-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.
A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with tulathromycin injection to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with tulathromycin injection. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of tulathromycin injection in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, tulathromycin injection is considered effective for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* in suckling calves, dairy calves, and veal calves.
In another multi-location field study with 399 calves at high risk of developing BRD, administration of tulathromycin injection resulted in a significantly reduced incidence of BRD (11%) compared to saline-treated calves (59%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. There were no BRD-related deaths in the tulathromycin injection-treated calves compared to two BRD-related deaths in the saline-treated calves. Fifty saline-treated calves classified as non-responders in this study had *Mycoplasma bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.
Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either tulathromycin injection (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the tulathromycin injection-treated calves compared with saline-treated calves (11.3% vs. 28.9%, P = 0.0001 and 15.0% vs. 30.7%, P < 0.0001).

IBK – Two field studies were conducted evaluating tulathromycin injection for the treatment of IBK associated with *Moraxella bovis* in 200 naturally-infected calves. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of IBK and no corneal ulcer, assessed on Days 5, 9, 13, 17, and 21. Time to improvement, defined as the first day on which a calf had no clinical signs of IBK in both eyes, provided that those scores were maintained at the next day of observation, was assessed as a secondary variable. At all time points, in both studies, the cure rate was significantly higher (P < 0.05) for tulathromycin injection-treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less (P < 0.0001) in both studies for tulathromycin injection-treated calves compared to saline-treated calves.

Foot Rot - The effectiveness of tulathromycin injection for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of tulathromycin injection (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, the treatment success percentage was statistically significantly higher in tulathromycin injection-treated calves compared with saline-treated calves (60% vs. 8%, P < 0.0001 and 83.3% vs. 50%, P = 0.0088).

Swine
In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with tulathromycin injection. Responses to treatment were compared to saline-treated controls. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F on Day 7. The treatment success rate was significantly greater (P ≤ 0.05) in tulathromycin injection-treated pigs (70.5%) compared to saline-treated pigs (46.1%). *M. hyopneumoniae* was isolated from 106 saline-treated and non-treated sentinel pigs in this study.
Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection against *M. hyopneumoniae*. Ten days after inoculation intranasally and intratracheally with a field strain of *M. hyopneumoniae*, 144 pigs were treated with either tulathromycin injection (2.5 mg/kg BW) intramuscularly or an equivalent volume of saline. Pigs were euthanized and necropsied 10 days post-treatment. The mean percentage of gross pneumonic lung lesions was statistically significantly lower (P < 0.0001) for tulathromycin injection-treated pigs than for saline-treated pigs in both studies (8.52% vs. 23.62% and 11.31% vs. 26.42%).
The effectiveness of tulathromycin injection for the control of SRD was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, all pigs were enrolled and treated with tulathromycin injection (226 pigs) or saline (227 pigs). Responses to treatment were evaluated on Day 7. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F. The treatment success rate was significantly greater (P < 0.05) in tulathromycin injection-treated pigs compared to saline-treated pigs (59.2% vs. 41.2%).

ANIMAL SAFETY

Cattle
Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups.These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically.
An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15 mg/kg BW.
A safety study was conducted in preruminant calves 13 to 27 days of age receiving 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

Swine
Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.

STORAGE CONDITIONS
Store at or below 30°C (86°F). Use within 45 days of first puncture and puncture a maximum of 20 times. Consider using automatic injection equipment or a repeater syringe. When using a needle or draw-off spike larger than 16 gauge, discard any remaining product immediately after use.

HOW SUPPLIED: TULISSIN 100 Injectable Solution is available in the following package sizes:
50 mL vial ; 100 mL vial ; 250 mL vial ; 500 mL vial

Manufactured for: Virbac AH, Inc. - P.O. Box 162059, Fort Worth, TX 76161 - Made in France

Approved by FDA under ANADA # 200-669

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

Rev. 06/22

TAKE TIME OBSERVE LABEL DIRECTIONS

Virbac

Tulissin®-25-

(tulathromycin injection)
Injectable Solution

Antibiotic
25 mg of tulathromycin/mL
For use in suckling calves, dairy calves, veal calves, and swine. Not for use in ruminating cattle.

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

DESCRIPTION
TULISSIN 25 Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of TULISSIN 25 contains 25 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (5 mg/mL), citric acid (4.8 mg/mL) with hydrochloric acid and sodium hydroxide added to adjust pH. TULISSIN 25 consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio.

The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl]-α-L-ribohexopyrano-syl] oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-met hyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribohexopyrano-syl] oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-xylohexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Swine
TULISSIN 25 Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis,* and *Mycoplasma hyopneumoniae*; and for the control of SRD associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.

Suckling Calves, Dairy Calves, and Veal Calves
BRD - TULISSIN 25 Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis.*

DOSAGE AND ADMINISTRATION

Swine
Inject intramuscularly as a single dose in the neck at a dosage of 2.5 mg/kg (1 mL/22 lb) Body Weight (BW). Do not inject more than 4 mL per injection site.

Table 1. TULISSIN 25 Injectable Solution Swine Dosing Guide (25 mg/mL)

Animal Weight (Pounds)	Dose Volume (mL)
4	0.2
10	0.5
15	0.7
20	0.9
22	1.0
25	1.1
30	1.4
50	2.3
70	3.2
90	4.0

Calves
Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1 mL/22 lb) body weight (BW). Do not inject more than 11.5 mL per injection site.

Table 2. TULISSIN 25 Injectable Solution Calf Dosing Guide (25 mg/mL)

Animal Weight (Pounds)	Dose Volume (mL)
50	2.3
75	3.4
100	4.5
150	7.0
200	9.0
250	11.5

CONTRAINDICATIONS
The use of TULISSIN 25 Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS
FOR USE IN ANIMALS ONLY.
NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS

Swine
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

Calves
Calves intended for human consumption must not be slaughtered within 22 days from the last treatment with TULISSIN 25 Injectable Solution. This drug is not for use in ruminating cattle.

PRECAUTIONS

Swine
The effects of Tulissin 25 Injectable Solution on porcine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

Cattle
The effects of Tulissin 25 Injectable Solution on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS

Swine
In one field study, one out of 40 pigs treated with tulathromycin injection (100 mg/mL) at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

Calves
In one BRD field study, two calves treated with tulathromycin injection (100 mg/mL) at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

Post Approval Experience
The following adverse events are based on post approval adverse drug experience reporting for tulathromycin injection (100 mg/mL). Not all adverse events are reported to the 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 following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. 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
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than lipophilic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lung parenchyma as compared to the plasma, and these elevated concentrations can remain in lung tissue for several days beyond that which can be measured in the plasma. However the clinical relevance of these elevated lung concentrations is undetermined.

As a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] When acting as a cidal compound, they tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration.[3] Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

[1] *Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis.,* ***27****:28-32.*
[2] *Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J.,* ***16****:438-443.*
[3] *Andes D, Anon J, Jacobs MR, Craig WA. (2004). Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. Clin Lab Med.,* ***24****:477-502.*

Swine
Following intramuscular (IM) administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is nearly completely absorbed, with peak plasma concentrations achieved within ~0.25 hr. The volume of distribution exceeds 15 L/kg, which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half-life (60 to 90 hours) despite a rapid systemic free drug clearance (187 mL/kg/hr). There are no gender differences in swine tulathromycin pharmacokinetics.

Comparative Bioavailability Summary
Despite slightly lower peak concentrations with tulathromycin injection 25 mg/mL, a single IM dose of 2.5 mg tulathromycin/kg BW of either tulathromycin injection (100 mg/mL) or tulathromycin injection (25 mg/mL) resulted in comparable tulathromycin total systemic exposure. Therefore, tulathromycin injection 25 mg/mL is considered to be therapeutically equivalent to tulathromycin injection 100 mg/mL when administered to swine by IM injection at a dose of 2.5 mg tulathromycin/kg BW.

Calves
Following subcutaneous (SC) administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is nearly completely absorbed, with peak plasma concentrations achieved within ~0.25 hr. The volume of distribution exceeds 11 L/kg[4], which is consistent with extensive tissue binding. This large distribution volume results in a long terminal elimination half-life of more than 100 hours, despite a rapid systemic free drug clearance (170 mL/kg/hr). No pharmacokinetic differences are observed in castrated male versus female calves.

Comparative Bioavailability Summary
Despite lower peak concentrations with tulathromycin injection 25 mg/mL, a single SC dose of 2.5 mg tulathromycin/kg BW of either tulathromycin injection (100 mg/mL) or tulathromycin injection (25 mg/mL) resulted in comparable total systemic tulathromycin exposure. Therefore, tulathromycin injection 25 mg/mL is considered to be therapeutically equivalent to tulathromycin injection 100 mg/mL when administered to calves by SC injection at a dose of 2.5 mg tulathromycin/kg BW.

[4] Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

MICROBIOLOGY

Swine
Tulathromycin has demonstrated in vitro activity against *A. pleuropneumoniae, P. multocida, B. bronchiseptica, H. parasuis,* and *M. hyopneumoniae*. The MICs of tulathromycin against indicated pathogens collected from field studies were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for *H. parasuis* were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO_2-enriched atmosphere. These values are represented in Table 3, below.

Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating SRD in the U.S. and Canada.

Indicated Pathogen	Date isolated	No. of isolates	MIC_{50} † (µg/mL)	MIC_{90} † (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	2000-2002 2007-2008	135 88	16 16	32 16	16 to 32 4 to 32
Haemophilus parasuis	2000-2002	31	1	2	0.25 to > 64
Pasteurella multocida	2000-2002 2007-2008	55 40	1 1	2 2	0.5 to > 64 ≤ 0.03 to 2
Bordetella bronchiseptica	2000-2002	42	4	8	2 to 8

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
† The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Calves
Tulathromycin has demonstrated *in vitro* activity against *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*, four pathogens associated with BRD. The MICs of tulathromycin against indicated pathogens collected from field studies using tula thromycin injection (100 mg/mL) were determined using methods recommended by the CLSI (M31-A2). These values are represented in Table 4, below.

Table 4. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD in the U.S.

Indicated Pathogen	Date isolated	No. of isolates	MIC_{50} † (µg/mL)	MIC_{90} † (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	1999	43	0.125	1	≤ 0.063 to > 64

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
† The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS

Swine
Plasma concentrations of tulathromycin administered as tulathromycin injection (100 mg/mL) or as tulathromycin injection 25 mg/mL were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore, effectiveness studies conducted with tulathromycin injection (100 mg/mL) support the effectiveness for tulathromycin injection 25 mg/mL.
In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with tulathromycin injection (100 mg/mL). Responses to treatment were compared to saline-treated controls. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F on Day 7. The treatment success rate was significantly greater (P ≤ 0.05) in tulathromycin injection 100 mg/mL-treated pigs (70.5%) compared to saline-treated pigs (46.1%). *M. hyopneumoniae* was isolated from 106 saline-treated and non-treated sentinel pigs in this study.
Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection (100 mg/mL) against *M. hyopneumoniae*. Ten days after inoculation intranasally and intratracheally with a field strain of *M. hyopneumoniae*, 144 pigs were treated with either tulathromycin injection 100 mg/mL (2.5 mg/kg BW) intramuscularly or an equivalent volume of saline. Pigs were euthanized and necropsied 10 days post-treatment. The mean percentage of gross pneumonic lung lesions was statistically significantly lower (P < 0.0001) for tulathromycin injection 100 mg/mL-treated pigs than for saline-treated pigs in both studies (8.52% vs. 23.62% and 11.31% vs. 26.42%).
The effectiveness of tulathromycin injection (100 mg/mL) for the control of SRD was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, all pigs were enrolled and treated with tulathromycin injection 100 mg/mL (226 pigs) or saline (227 pigs). Responses to treatment were evaluated on Day 7. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F. The treatment success rate was significantly greater (P < 0.05) in tulathromycin injection 100 mg/mL-treated pigs compared to saline-treated pigs (59.2% vs. 41.2%).

Calves
Plasma concentrations of tulathromycin administered as tulathromycin injection (100 mg/mL) or as tulathromycin injection 25 mg/mL were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore, effectiveness studies conducted with tulathromycin injection (100 mg/mL) support the effectiveness for tulathromycin injection 25 mg/mL.

BRD - In a multi-location field study, 314 calves with naturally occurring BRD were treated with tulathromycin injection (100 mg/mL). Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. The cure rate was significantly higher (P ≤ 0.05) in tulathromycin injection 100 mg/mL-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the tulathromycin injection 100 mg/mL-treated calves compared to nine BRD-related deaths in the saline-treated calves.
Fifty-two tulathromycin injection (100 mg/mL)-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 tulathromycin injection 100 mg/mL-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.
A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with tulathromycin injection (100 mg/mL) to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with tulathromycin injection 100 mg/mL. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of tulathromycin injection (100 mg/mL) in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, tulathromycin injection (100 mg/mL) was considered effective for the treatment of BRD associated with *M. haemolytica, P. multocida, H. somni,* and *M. bovis* in suckling calves, dairy calves, and veal calves.
Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection (100 mg/mL) against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either tulathromycin injection 100 mg/mL (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the tulathromycin injection 100 mg/mL-treated calves compared with saline-treated calves (11.3% vs. 28.9%, P = 0.0001 and 15.0% vs. 30.7%, P < 0.0001).

ANIMAL SAFETY

Swine
Plasma concentrations of tulathromycin administered as tulathromycin injection (100 mg/mL) or as tulathromycin injection 25 mg/mL were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore, systemic target animal safety studies conducted with tulathromycin injection 100 mg/mL support the systemic safety for tulathromycin injection 25 mg/mL.
Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular doses of 2.5, 7.5, or 12.5 mg/kg BW (both studies utilized tulathromycin injection (100 mg/mL)). In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.
Sixteen growing pigs were injected with either saline or tulathromycin injection 25 mg/mL as a single injection of 4 mL. Injection site observations included two instances of erythema in the tulathromycin injection 25 mg/mL-treated group on Day 1 post-injection. No heat, sensitivity, firmness, necrosis, drainage, or swelling was observed at any injection sites in either treatment group. The gross and microscopic findings in the tulathromycin injection 25 mg/mL-treated group were consistent with inflammatory changes induced by injections and were considered to be mild or moderate with progression to macroscopic resolution by Day 28 post-injection and microscopic resolution by Day 42 post-injection.

Calves
Plasma concentrations of tulathromycin administered as tulathromycin injection (100 mg/mL) or as tulathromycin injection 25 mg/mL were demonstrated to be therapeutically equivalent (see CLINICAL PHARMACOLOGY, Comparative Bioavailability Summary). Therefore, systemic target animal safety studies conducted with tulathromycin injection 100 mg/mL support the systemic safety for tulathromycin injection 25 mg/mL.
A safety study was conducted in feeder calves receiving tulathromycin injection (100 mg/mL) as a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically.
An exploratory study was conducted in feeder calves receiving tulathromycin injection (100 mg/mL) as a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15 mg/kg BW.
A safety study was conducted in preruminant calves 13 to 27 days of age receiving tulathromycin injection (100 mg/mL) at 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.
Sixteen growing cattle were injected with either saline (eight animals) as a single injection of 11.5 mL or tulathromycin injection 25 mg/mL (eight animals) as a single injection of either 2.5 mg/kg BW or a dose volume of 11.5 mL (whichever volume was higher). One calf in the tulathromycin injection 25 mg/mL-treated group was observed to have firmness at the injection site for a single day. Two tulathromycin injection 25 mg/mL-treated calves exhibited injection site swelling. In one calf, the swelling resolved within 48 hours. In the other calf, the swelling was observed over a three-day period, after which the calf underwent a scheduled necropsy, preventing further injection site observations. No injection site swelling was observed in saline-treated animals. At necropsy, three of the saline-treated calves and five of the tulathromycin injection 25 mg/mL-treated calves had altered tissue present at the injection site. The gross and microscopic findings in the tulathromycin injection 25 mg/mL-treated group were consistent with inflammatory changes induced by injections, were considered to be mild to marked, and progressed to macroscopic resolution and microscopic resolution by Day 42 post-injection.

STORAGE CONDITIONS:
Store at or below 30°C (86°F). Use within 45 days of first puncture and puncture a maximum of 30 times. Consider using automatic injection equipment or a repeater syringe. When using a needle or draw-off spike larger than 16 gauge, discard any remaining product immediately after use.

HOW SUPPLIED
TULISSIN 25 (tulathromycin injection) Injectable Solution is available in the following package sizes:
50 mL vial
100 mL vial
250 mL vial

Manufactured for:
Virbac AH, Inc.
P.O. Box 162059, Fort Worth, TX 76161
Made in France

Approved by FDA under ANADA # 200-668

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

TAKE TIME OBSERVE LABEL DIRECTIONS

Rev. 06/21

PRODUCT INSERTS/DISCLOSURES

Human Warning:
Keep this and all medication out of reach of children. To obtain product information, including a Safety Data Sheet (SDS), call 1-800-338-3659.
301796 - 03

If you notice these signs, contact a veterinarian.

Directions:
Each flavored chewable contains 30 mg of pyrantel pamoate and 30 mg of praziquantel. The dose for each drug is 2.27 mg per pound of body weight (5 mg/kg). Please refer to the following dosing table for help finding the right dose for your dog.

Virbantel® Flavored Chewables

Package contents: bottle of 50 flavored chewables

Drug Facts

Active Ingredients (in each chewable):
pyrantel pamoate (30 mg) and praziquantel (30 mg)

Purpose: De-wormer for Small Dogs and Puppies Only (6.0 to 25 pounds).

Uses: For the treatment and control of:
- Roundworms (*Toxocara canis, Toxascaris leonina*)
- Hookworms (*Ancylostoma caninum, Ancylostoma braziliense*, and *Uncinaria stenocephala*)
- Tapeworms (*Dipylidium caninum, Taenia pisiformis*)

Human Warning:
Keep this and all medication out of the reach of children. To obtain product information, including a Safety Data Sheet (SDS), call 1-800-338-3659.

When Using This Product:
- Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.
- Do not de-worm a dog or puppy that is sick. Consult a veterinarian for diagnosis of the illness.
- **VIRBANTEL** Flavored Chewables are safe for use in puppies 12 weeks or older and adult dogs. Safety in breeding dogs and pregnant bitches has not been tested.

You May Notice:
Vomiting, loose stools (with or without blood) and decreased activity following treatment.

VIRBANTEL® Flavored Chewables Dosing Table

Dog Weight / Number of Chewables
6.0 to 12 pounds: 1 Chewable
12.1 to 25 pounds: 2 Chewables
More than 25 pounds: Use 114 mg size.

- You should weigh your dog to make sure you are giving the right dose.
- **VIRBANTEL** Flavored Chewables are palatable if offered by hand. If your dog does not voluntarily eat the chewable, you can hide the chewable in a small amount of food or place it in the back of the dog's mouth for forced swallowing.
- Make sure that the dog eats the complete dose.
- Watch your dog for a few minutes after dosing to make sure the chewable is not rejected.

Other Information:
Recommended De-Worming Schedule:
Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism. De-worming schedules may vary depending on the climate where you live and the activity of your dog.

Re-treatment: Re-treatment of your dog may be necessary as determined by laboratory fecal examination and/or if your dog is living where re-infections are likely to occur. Consult your veterinarian for assistance in the diagnosis and prevention of re-infection. In case of re-infection with tapeworms (*Dipylidium caninum*), consult your veterinarian for advice on how to remove fleas from the dog and the environment.

Manufactured by:
Virbac AH, Inc.
Fort Worth, TX 76137
Storage: Store at controlled room temperature of 59 - 86˚F (15 - 30˚C).

Questions? Comments?
To report a suspected adverse reaction, call 1-800-338-3659.

02/19 301798 - 03

Approved by FDA under NADA # 141-261

Virbantel® Flavored Chewables

Package contents: bottle of 50 flavored chewables

Drug Facts

Active Ingredients (in each chewable):
pyrantel pamoate (114 mg) and praziquantel (114 mg)

Purpose: De-wormer for Medium and Large Dogs Only (Greater than 25 pounds).

Uses: For the treatment and control of:
- Roundworms (*Toxocara canis, Toxascaris leonina*)
- Hookworms (*Ancylostoma caninum, Ancylostoma braziliense*, and *Uncinaria stenocephala*)
- Tapeworms (*Dipylidium caninum, Taenia pisiformis*)

When Using This Product:
- Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.
- Do not de-worm a dog or puppy that is sick. Consult a veterinarian for diagnosis of the illness.
- **VIRBANTEL** Flavored Chewables are safe for use in puppies 12 weeks or older and adult dogs. Safety in breeding dogs and pregnant bitches has not been tested.

You May Notice:
Vomiting, loose stools (with or without blood) and decreased activity following treatment. If you notice these signs, contact a veterinarian.

Human Warning:
Keep this and all medication out of the reach of children. To obtain product information, including a Safety Data Sheet (SDS), call 1-800-338-3659.

Other Information:
Recommended De-Worming Schedule:
Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism. De-worming schedules may vary depending on the climate where you live and the activity of your dog.

Re-treatment: Re-treatment of your dog may be necessary as determined by laboratory fecal examination and/or if your dog is living where re-infections are likely to occur. Consult your veterinarian for assistance in the diagnosis and prevention of re-infection. In case of re-infection with tapeworms (*Dipylidium caninum*), consult your veterinarian for advice on how to remove fleas from the dog and the environment.

Directions: Each flavored chewable contains 114 mg of pyrantel pamoate and 114 mg of praziquantel. The dose for each drug is 2.27 mg per pound of body weight (5 mg/kg). Please refer to the following dosing table for help finding the right dose for your dog.

VIRBANTEL Flavored Chewables Dosing Table

Dog Weight	Number of Chewables
6.0 to 25 pounds	Use the 30 mg size.
25.1 to 50 pounds	1
50.1 to 100 pounds	2
100.1 to 150 pounds	3
150.1 to 200 pounds	4

Manufactured by:
Virbac AH, Inc.
Fort Worth, TX 76137

Storage:
Store at controlled room temperature of 59 - 86˚F (15 - 30˚C).

Questions? Comments?
To report a suspected adverse reaction, call 1-800-338-3659.

2/2019 301799-03

Approved by FDA under NADA # 141-261

Virbac

ZOLETIL®

(tiletamine and zolazepam for injection)

100 mg/mL total
(equivalent to 50 mg/mL tiletamine and 50 mg/mL zolazepam)
For Intramuscular and Intravenous Injection in Dogs
For Intramuscular injection only in Cats

CAUTION

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

DESCRIPTION

Zoletil® (tiletamine and zolazepam for injection) is a nonnarcotic, nonbarbiturate, injectable anesthetic agent for dogs and cats. Chemically, ZOLETIL is a combination of equal parts by weight of base of tiletamine hydrochloride (2-[ethylamino]-2- [2-thienyl]- cyclohexanone hydrochloride), an arylaminocycloalkanone dissociative anesthetic, and zolazepam hydrochloride (4-[o-fluorophenyl]-6, 8-dihydro-1,3,8-trimethylpyrazolo [3,4-e] [1,4] diazepin-7 [1H]-1-hydrochloride), a nonphenothiazine diazepinone having minor tranquilizing properties. The product is supplied sterile in vials. The addition of 5 mL diluent produces a solution containing the equivalent of 50 mg tiletamine base, 50 mg zolazepam base and 57.7 mg mannitol per milliliter. This solution has a pH of 2 to 3.5 and is recommended for deep intramuscular injection.

INDICATIONS

Dogs

ZOLETIL is indicated in dogs for restraint and minor procedures of short duration (30 min. avg.) requiring mild to moderate analgesia. Minor surgery is considered to be laceration repair, draining of abscesses, castrations and other procedures requiring mild to moderate analgesia. (See **Dogs** under **DOSAGE AND ADMINISTRATION**.)

ZOLETIL administered intravenously is indicated in dogs for induction of anesthesia followed by maintenance with an inhalant anesthetic.

Cats

ZOLETIL is indicated in cats for restraint or for anesthesia combined with muscle relaxation.

DOSAGE AND ADMINISTRATION

The dose is determined by the total combined concentration of 100 mg/mL (see HOW SUPPLIED)

Dogs

Intramuscular (IM) For Restraint and Minor Procedures of Short Duration Requiring Mild to Moderate Analgesia:

In healthy dogs, an initial intramuscular dosage of 3 to 4.5 mg/lb (6.6 to 9.9 mg/kg) ZOLETIL is recommended for diagnostic purposes; 4.5 to 6 mg/lb (9.9 to 13.2 mg/kg) for minor procedures of short duration, such as treatment of lacerations and wounds, castrations and other procedures requiring mild to moderate analgesia. When supplemental doses of ZOLETIL are required, such individual supplemental doses should be less than the initial dose, and the total dose given (initial dose plus supplemental dose or doses) should not exceed 12 mg/lb (26.4 mg/kg). The maximum safe dose is 13.6 mg/lb (29.92 mg/kg). (See **ANIMAL SAFETY**) Results from ZOLETIL anesthesia in dogs will be more satisfactory if the procedures are completed within one hour and if the procedures can be completed following single dose administration. In order to maintain at least a 2X margin of safety in dogs, the use of this product is limited to procedures that call for low doses (see **INDICATIONS**). Studies show that there is variation in response to different dosages of tiletamine and zolazepam for injection and that low doses do not give adequate levels of anesthesia, and in some instances do not give adequate analgesia, for extensive procedures.

Intravenous (IV) For Induction of Anesthesia Followed by Maintenance with an Inhalant Anesthetic:

In dogs, for induction of anesthesia, administer ZOLETIL intravenously at 1-2 mg/lb (2.2-4.4 mg/kg) body weight to effect. ZOLETIL should be administered slowly, over 30-45 seconds; after approximately 30-60 seconds, the dog's level of consciousness, muscle relaxation, and jaw tone should be assessed to determine the ability to intubate. If after waiting 60 seconds the dog's level of anesthesia is not sufficient for successful intubation, additional ZOLETIL may be administered; the total dose should not exceed 2 mg/lb (4.4 mg/kg) body weight.

Cats

In healthy cats, an initial ZOLETIL dosage of 4.4 to 5.4 mg/lb (9.7 to 11.9 mg/kg) IM is recommended for such procedures as dentistry, treatment of abscesses, foreign body removal and related types of surgery; 4.8 to 5.7 mg/lb (10.6 to 12.5 mg/kg) for minor procedures requiring mild to moderate analgesia, such as repair of lacerations, castrations and other procedures of short duration. Initial dosages of 6.5 to 7.2 mg/lb (14.3 to 15.8 mg/kg) are recommended for ovariohysterectomy and onychectomy. When supplemental doses of ZOLETIL are required, such individual supplemental doses should be given in increments that are less than the initial dose, and the total dose given (initial dose plus supplemental doses) should not exceed the maximum allowable safe dose of 32.7 mg/lb (72 mg/kg). (See **ANIMAL SAFETY**)

General Dosing Information

Fasting prior to induction of general anesthesia with ZOLETIL is not essential; however, when preparing for elective surgery, it is advisable to withhold food for at least 12 hours prior to ZOLETIL administration. As with other injectable anesthetic agents, the individual response to ZOLETIL is somewhat varied, depending upon the dose, general physical condition and age of the patient, duration of the surgical procedure, and any preanesthetics used. Therefore, recommendations for dosage regimens cannot be fixed absolutely. Specific dosage requirements must be determined by evaluation of the health status and condition of the patient and of the procedure to be performed.

Recovery varies with the age and physical condition of the animal and the dose of ZOLETIL administered. Recovery is extended with high dose or multiple injections, particularly in cats.

Intramuscular injection in dogs and cats:

There may be pain on injection. This is especially prevalent in cats.

Following a single, deep intramuscular injection of ZOLETIL in cats and dogs, onset of anesthetic effect usually occurs within 5 to 12 minutes. Muscle relaxation is optimum for approximately the first 20 to 25 minutes after ZOLETIL is administered, and then diminishes.

Repeated doses increase the duration of the effect of ZOLETIL but may not further diminish muscle tone. The quality of anesthesia with repeated doses varies because the ratio of the two components within the animal's body changes with each injection. This is due to the difference in the rates of metabolism and elimination of the two components. The quality of anesthesia will be improved and more predictable if the entire dose is given as a single injection rather than in several doses. The best method of evaluating the depth of ZOLETIL anesthesia is to monitor the patient for deliberate conscious response to nociceptive stimuli.

If adequate anesthesia is not produced by the recommended dosage regimen, supplemental anesthesia or another agent is indicated. This includes the use of barbiturates and volatile anesthetics. When used concurrently with ZOLETIL the dosage of these agents should be reduced.

PREPARATION OF SOLUTION FOR ADMINISTRATION

To each vial add 5 mL sterile water for injection, USP. Slight agitation will facilitate complete reconstitution. The resultant solution will contain 100 mg total ZOLETIL per one milliliter (50 mg tiletamine and 50 mg zolazepam per mL).

Discard unused solution after 4 days when stored at room temperature or after 14 days when kept refrigerated. Only use clear solution. Color of solution may vary from colorless to light amber.

CONTRAINDICATIONS

The use of ZOLETIL is contraindicated in dogs and cats with pancreatic disease. ZOLETIL should not be used in dogs and cats with severe cardiac or pulmonary dysfunction.

Because the teratogenic potential of ZOLETIL is unknown, it should not be used in pregnant bitches or queens at any stage of pregnancy. Also, a study has shown that tiletamine and zolazepam for injection crosses the placental barrier and produces respiratory depression in the newborn; therefore, its use for Cesarean section is contraindicated.

WARNINGS

FOR USE IN DOGS AND CATS ONLY.

When using ZOLETIL for induction of anesthesia, patients should be continuously monitored. Facilities for the maintenance of a patent airway, artificial ventilation and oxygen supplementation should be available.

Pulmonary edema has been reported to occur in cats with the use of tiletamine and zolazepam for injection. Signs and symptoms include dyspnea, lethargy, anorexia and abnormal behavior. Deaths have been reported occasionally in severely affected individuals. Cats should be observed closely for any signs and symptoms which may suggest pulmonary edema so that appropriate therapy may be instituted.

The principal route of excretion of both components in the cat is the urine; therefore, ZOLETIL is not recommended for use in cats suffering from renal insufficiency.

Balance studies in dogs indicated extensive biotransformation of both components with less than 4% of the dose excreted unchanged in the urine.

ZOLETIL is excreted predominantly by the kidneys. Preexistent renal pathology or impairment of renal function may be expected to result in prolonged duration of anesthesia.

Phenothiazine-derivative drugs should not be used with ZOLETIL at dosages indicated for intramuscular (IM) injection because the combination produces respiratory and myocardial depression, hypotension and hypothermia.

The safe use of ZOLETIL in pregnant animals or on reproduction has not been established. ZOLETIL crosses the placental barrier and causes respiratory depression in the neonate.

PRECAUTIONS

The dosage of ZOLETIL should be reduced in geriatric dogs and cats, in animals in debilitated condition and in animals with impairment of renal function. Death has occurred in both cats and dogs following intramuscular tiletamine and zolazepam for injection administration. Preexisting pulmonary disease, renal disease (see **CONTRAINDICATIONS** and **WARNINGS**) and shock were causally implicated at necropsy; however, death was drug attributable in at least one dog (of 1072) and one cat (of 1095).

Intravenous tiletamine and zolazepam for injection has been demonstrated to be safe in a field study in dogs when used in conjunction with phenothiazine-derivative drugs (acepromazine) administered at dosages from 0.04-0.06 mg/kg IM.

Cats and smaller dogs with small body masses in relation to large body surfaces should be protected from heat loss during ZOLETIL anesthesia. Body temperature should be monitored, and supplemental heat may be required to control hypothermia. As with other anesthetics, it is prudent to provide for hemostasis during any surgical procedure.

During ZOLETIL anesthesia, athetoid movement may occur. This athetosis should not be mistaken for lack of anesthesia nor is it indicative of lack of analgesia. Do not give additional anesthesia in an attempt to abolish the athetoid movement. Efforts to eliminate athetoid movement with additional doses of ZOLETIL can result in anesthetic overdosage.

ZOLETIL does not abolish laryngeal, pharyngeal, pinnal, palpebral, and pedal reflexes, and may not be adequate as the sole anesthetic for surgical procedures in these areas. Endotracheal tubes are not well tolerated in connection with ZOLETIL anesthesia in the cat and their use may result in impaired respiration. After removal of the tube, normal respiration should resume.

The stimulation of surgical procedures aids in maintaining adequate ventilation. The anesthetized patient must be monitored throughout the procedure, and if cardiopulmonary problems do occur, measures must be taken to assure that alveolar ventilation and cardiovascular functions are maintained.

The eyes normally remain open with the pupils dilated. The use of a bland ophthalmic ointment is advisable to protect the corneas from desiccation. The concurrent use of chloramphenicol will prolong the duration of anesthesia in cats.

Copious salivation may occur during ZOLETIL anesthesia. Ptyalism may be controlled in dogs and cats by administering atropine sulfate, USP, 0.02 mg/lb (0.04 mg/kg) body weight (IV, IM, or SC) as concurrent medication. Exaggerated swallowing, reflex action and accumulation of saliva may give rise to vomiting and retching.

ADVERSE REACTIONS

For Restraint and Minor Procedures of Short Duration Requiring Mild to Moderate Analgesia

Respiratory depression may occur following administration of high doses of ZOLETIL. If at any time respiration becomes excessively depressed and the animal becomes cyanotic, resuscitative measures should be instituted promptly. Adequate pulmonary ventilation using either oxygen or room air is recommended as a resuscitative measure.

Adverse reactions reported include emesis during emergence, excessive salivation, transient apnea, vocalization, erratic recovery and prolonged recovery, excessive tracheal and bronchial secretions when atropine sulfate was not given before anesthesia, involuntary muscular twitching, hypertonicity, cyanosis, cardiac arrest, pulmonary edema and muscle rigidity during surgical procedures. Central nervous system stimulation and convulsions have also been reported. Tachycardia frequently occurs, particularly in the dog. This rise in heart rate usually lasts about 30 minutes. Either hypertension or hypotension may also occur. Insufficient anesthesia has been reported in dogs. Death has been reported in dogs and cats following tiletamine and zolazepam for injection administration.

Intravenous Induction of Anesthesia followed by Maintenance with Inhalant Anesthesia in Dogs

In a field study to assess the effectiveness and safety of tiletamine and zolazepam for injection administered intravenously at 1-2 mg/lb (2.2-4.4 mg/kg) for the induction of anesthesia followed by maintenance with inhalant anesthesia in dogs, 144 dogs were intravenously administered tiletamine and zolazepam for injection (See **EFFECTIVENESS**). Sixteen adverse reactions occurred during the study: nystagmus (5), emesis (4), diarrhea (2), and one occurrence each of hypersalivation, urticaria, anorexia, hyperthermia, and lethargy. All adverse reactions resolved by the end of the study.

Physiologic abnormalities related to general anesthesia were transient and not severe.

Post-induction apnea (time from induction to first inspiration ≥30 seconds) was observed in 49.3% of dogs across all treatment groups with a mean duration of one minute. The highest overall frequency and duration of post-induction apnea was in the alpha$_2$-agonist + opioid groups.

Overall, 36 dogs received assisted ventilation. Assisted ventilation was needed most frequently early in the procedure (at procedure start, possibly after an apneic period) then decreased in frequency as the procedure continued.

Sixteen dogs experienced oxygen saturation (SpO_2) ≤90 mmHg: 7 in the alpha$_2$-agonist + opioid groups, 6 in the phenothiazine + opioid groups, and 3 in the opioid alone groups.

Twenty-five dogs had a temperature ≥103°F during the study, with 12 of these occurring prior to preanesthetic administration only. Of the remaining 13 dogs, 7 were in the alpha$_2$-agonist + opioid groups, 5 were in the opioid alone groups, and 1 in the phenothiazine + opioid groups. One dog was reported with hyperthermia as an adverse reaction in the alpha$_2$-agonist + opioid treatment groups. The dog became excitable during recovery and its temperature elevated to 105.7°F. Hyperthermia resolved with treatment of IV fluids and cooling.

Twenty-seven dogs experienced temperatures ≤96°F at one or more timepoints. Most dogs received supplemental heat during surgery.

Fifty-nine dogs had mean blood pressure (BP) values ≤60 mmHg. These values are spread among all treatment groups. No dogs were reported with adverse reactions due to hypotension or hypertension in any dose groups. Elevated or low BP values were transient.

Ventricular premature depolarizations were noted in 3 dogs in the alpha$_2$-agonist + opioid group. This transient rhythm disturbance is not uncommon in dogs receiving alpha$_2$-agonists or inhalant anesthetics. One dog in the phenothiazine + opioid group showed transient ST depression that could have been due to cardiac hypoxia. All dogs recovered normally.

To report suspected adverse drug events or for technical assistance contact Virbac AH, Inc. at 1-800-338-3659. Visit vet-us.virbac.com for product details.

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.

CLINICAL PHARMACOLOGY

Mechanism of Action

ZOLETIL® (tiletamine and zolazepam for injection) is a rapid-acting anesthetic combination of tiletamine hydrochloride and zolazepam hydrochloride. Tiletamine hydrochloride is a dissociative anesthetic agent whose pharmacologic action is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes and cataleptoid anesthesia.

The anesthetic state produced does not fit into the conventional classification of stages of anesthesia, but instead ZOLETIL produces a state of unconsciousness which has been termed "dissociative" anesthesia in that it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade.

Cranial nerve and spinal reflexes remain active; however, these reflexes must not be confused with inadequate anesthesia. Analgesia results from apparent selective interruption of sensory inputs to the brain and usually persists after the anesthetic effect has subsided.

Protective reflexes, such as coughing and swallowing, are maintained under tiletamine anesthesia. Other reflexes, e.g., corneal, pedal, are maintained during tiletamine anesthesia, and should not be used as criteria for judging depth of anesthesia. The eyes normally remain open with the pupil dilated. It is suggested that a bland ophthalmic ointment be applied to the cornea if anesthesia is to be prolonged.

Used alone, tiletamine hydrochloride does not provide adequate muscle relaxation for abdominal surgical procedures. When combined with zolazepam hydrochloride, good muscle relaxation is generally attained during the phase of deep surgical anesthesia.

Pharmacokinetics

The pharmacokinetics of tiletamine and zolazepam for injection, injectable solution was evaluated in 12 healthy adult Beagle dogs, following a single intravenous (IV) administration of 2.2 mg/kg bodyweight, which is equivalent to 1.1 mg/kg for both tiletamine hydrochloride and zolazepam hydrochloride. After administration of 2.2 mg/kg tiletamine and zolazepam for injection IV, the initial mean concentration of tiletamine (C_0) was 1018 ng/mL, the systemic clearance (CL) was 6223 mL/kg/h, the area under the curve to the last measured concentration (AUC_{0-last}) was 178 ng*hr/mL, and steady state volume of distribution (V_{ss}) was 3250 mL/kg. The mean elimination half-life of tiletamine was 0.87 hours. For zolazepam, the mean C_0 was 2594 ng/mL, CL was 1993 mL/kg/h and V_{ss} was 604 mL/kg. The mean elimination half-life of zolazepam was 0.41 hours. The mean C_0 and AUC_{0-last} were approximately 2.5 and 3 times, respectively, greater for zolazepam than for tiletamine. However, the mean half-life ($T_{1/2}$) of tiletamine was approximately 2.5 times longer than for zolazepam, resulting in quantifiable plasma concentrations up to 2 hours longer.

Pretreatment with an alpha$_2$-agonist or phenothiazine followed by inhalant isoflurane has been shown to increase in the initial concentration of both tiletamine and zolazepam.

EFFECTIVENESS

Dogs

Preanesthesia

In a field study conducted at 6 veterinary hospitals, 144 dogs of various breeds, ranging in age from 4 months to 14 years (mean age 5 years) and body weights from 1.2- 85.5 kg, were enrolled for completion of a veterinary procedure requiring anesthesia. Dogs were preanesthetized with a phenothiazine + opioid, an opioid alone, or an alpha$_2$-agonist + opioid at the study Investigator's discretion based on individual patient needs. Approximately 20 minutes later, dogs were intravenously administered tiletamine and zolazepam for injection at 1-2 mg/lb (2.2-4.4 mg/kg) 'to effect' of anesthesia and were intubated. After induction, dogs received either isoflurane or sevoflurane for anesthetic maintenance for at least 30 minutes. Procedures conducted included dental prophylaxis with or without extractions (64), ovariohysterectomy (31), castration (18), and mass removal (14). Upon completion of the procedure, dogs were monitored to recovery for 4 hours, then followed at home for 2-4 days, monitoring for the presence of abnormal clinical signs.

Of 144 dogs enrolled in the study, 142 (98.6%) were successfully intubated after intravenous administration of tiletamine and zolazepam for injection at a mean dosage of 1.2 mg/lb (2.7 mg/kg). The mean dosage range was lowest in the alpha$_2$-agonist + opioid preanesthetic treatment group (0.9 mg/lb; 2 mg/kg) and highest in the opioid alone preanesthetic group (1.8 mg/lb; 3.9 mg/kg).

Overall induction quality evaluated on a scale of acceptable, intermediate, or unacceptable was acceptable in 131/143 (91.6%) dogs and intermediate in 12/143 (8.4%) dogs. On a scale of good, fair, or poor, study participants rated the quality of recovery from anesthesia as good in 75% of dogs (108/144) and fair in 18.1% (26/144). In an overall assessment of anesthesia, considering induction, maintenance, and recovery, was scored as excellent or good in 128/144 (88.9%) of dogs. Three dogs (2.1%) were rated with an overall assessment of anesthesia as poor, and for these dogs, recovery was also rated poor. Physiologic measurements of heart rate, respiratory rate, body temperature, oxygen saturation, and blood pressure during anesthetic induction, maintenance, and recovery showed that the administration of tiletamine and zolazepam for injection did not severely impact these variables. A variety of concomitant treatments were used during the study including intravenous fluid solutions, non-steroidal anti-inflammatory medications, antimicrobials, and antiparasitics that were consistent with routine canine practice.

ANIMAL SAFETY

Tiletamine and zolazepam for injection has a wider margin of safety in cats than in dogs. Dogs have survived repeated IM dosage regimens of 13.6 mg/lb (30 mg/kg) (maximum safe dose) for eight successive days. This is approximately two times the maximum recommended therapeutic dose. Cats have survived IM dosage regimens of up to 32.7 mg/lb (72 mg/kg) (maximum safe dose) on alternate days for seven episodes. This is 4.6 times the maximum recommended therapeutic dose for cats. However, these reports should not obviate prudent anesthetic practices. Some degree of tolerance has been reported. This tolerance appears to be species-variable.

Cats

In cats, the duration of effect of zolazepam exceeds that of tiletamine so that as the animal recovers there is a greater degree of tranquilization than anesthetization. There is a slight lowering of blood pressure during the first hour after injection. Heart rate and electrocardiogram readings are unaffected by tiletamine and zolazepam for injection. Arterial pO_2 levels are decreased three minutes after injection but usually return to normal within 15 to 35 minutes.

Dogs

In dogs, the duration of effect of tiletamine exceeds that of zolazepam so there is a lesser degree of tranquilization than anesthetization in this species. The total effect of tiletamine and zolazepam for injection in dogs is of shorter duration than in cats.

Following administration of tiletamine and zolazepam for injection in dogs, a marked, persistent tachycardia occurs within two minutes following either 4.5 or 9 mg/lb (10 or 20 mg/kg) tiletamine and zolazepam for injection intramuscularly. Stroke volume decreases proportionately to the increased rate at the 4.5 mg/lb (10 mg/kg) dose, with little change in net cardiac output. There is an initial increase in systolic blood pressure, with a slight drop in pressure within five minutes. The systolic blood pressure remains at this decreased level throughout the duration of the anesthetic effect. Diastolic pressure increases throughout this same period. Following a 9 mg/lb (20 mg/kg) dose of tiletamine and zolazepam for injection in dogs, the relationship between stroke volume and heart rate is disproportionate, with a resultant substantial decrease in cardiac output. Contractility and mean blood pressure are decreased, indicating direct myocardial depression. Ventricular function is adequate. During surgical manipulations, tachycardia and hypertension may be observed, and may be brought on by sympathetic reaction to painful stimuli. Epinephrine is markedly less arrhythmogenic in animals under tiletamine and zolazepam for injection anesthesia than in those under halothane anesthesia.

During tiletamine and zolazepam for injection anesthesia, the assurance of a patent airway is greatly enhanced by virtue of maintaining pharyngeal-laryngeal reflexes. During the first 15 minutes after intramuscular administration of 9 mg/lb (20 mg/kg) of tiletamine and zolazepam for injection, the respiratory rate is doubled while the tidal volume is decreased to less than one-half of control values. Arterial pO_2 levels also decrease. This may be evidenced by hypoxemia and cyanosis. The pulmonary function usually returns to normal within 35 minutes after the administration of tiletamine and zolazepam for injection.

Preanesthetic Compatibility Study in Dogs

Six healthy Beagle dogs (3 males and 3 females), at least 8 months of age, ranging in body weight between 5.6 and 9.4 kg, were fitted with a telemetry device that captured systemic arterial blood pressures, electrocardiogram, and body temperature. Each dog received a total of 6 treatments with at least a 7-day washout between periods. During each period, dogs received 1 of the following 6 preanesthetics prior to the tiletamine and zolazepam for injection administration: placebo (0.9% saline), acepromazine low dose (0.1 mg/kg body weight (BW)), acepromazine high dose (1.1 mg/kg BW), dexmedetomidine low dose (125 mcg/m^2 body surface area (BSA)), dexmedetomidine high dose (375 mcg/m^2 BSA), or butorphanol (0.4 mg/kg BW). Blood samples were collected at intubation, end of isoflurane administration, and after anesthesia when the dogs were able to walk. Plasma concentrations of tiletamine and zolazepam were measured using a validated method. Preanesthetic treatment with high dose acepromazine and both high and low doses of dexmedetomidine resulted in substantial increases in plasma concentrations of tiletamine and zolazepam at intubation. The increase in the tiletamine plasma concentrations was approximately 2X higher for the high dose of acepromazine and 2.7 to 4.5X higher for the low and high doses of dexmedetomidine, respectively, compared to saline. The increase in zolazepam plasma concentrations was 1.5X higher for the high dose acepromazine, and 1.8 to 2.8X higher for the low and high doses of dexmedetomidine, respectively, compared to saline.

No information on the dose-sparing of tiletamine and zolazepam for injection was obtained during the study because the dogs were given the full initial half-dose (2.2 mg/kg) and not actually administered tiletamine and zolazepam for injection 'to effect'. The average total dose of test article administered to the dogs was 2.6 mg/kg for the saline group and 2.2 mg/kg for the other treatment groups. One dog (saline group) required more than the initial 2.2 mg/kg bolus to achieve intubation at the first attempt.

Without preanesthesia (saline group), dogs retained a strong cough reflex, chewing motions, tachycardia and increased muscle tone during intubation. With preanesthesia, half of the dogs in the high dose dexmedetomidine group had no laryngeal reflex response to intubation and all experienced post-intubation apnea. The post-intubation apnea suggests that the 2.2 mg/kg dose of tiletamine and zolazepam for injection was higher than necessary in some groups.

All dogs in all treatment groups achieved successful anesthetic plane following tiletamine and zolazepam for injection administration and were intubated and induced to isoflurane anesthesia uneventfully. The quality of intubation, and occurrence and severity of adverse reactions (e.g., apnea and bradypnea) following tiletamine and zolazepam for injection administration and intubation revealed differences among preanesthetic treatment groups. The cardiovascular and respiratory changes observed were typical of each preanesthetic medication used in combination with tiletamine and zolazepam for injection. Acepromazine and isoflurane administration decreased arterial blood pressure. Dexmedetomidine decreased heart rate. Intubation transiently increased heart rate and/or blood pressure (sympathetic stimulations). Mild to severe respiratory depression was observed after tiletamine and zolazepam for injection administration and each preanesthetic agent. Adverse reactions were manageable with appropriate care.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25° C (68° to 77° F). Discard unused solution after 4 days when stored at room temperature or after 14 days when kept refrigerated. Only use clear solution. Color of solution may vary from colorless to light amber.

HOW SUPPLIED

ZOLETIL (tiletamine and zolazepam for injection) is available in individual vials of 5 mL solution when reconstituted. The addition of 5 mL diluent produces a solution containing the equivalent of 50 mg tiletamine base, 50 mg zolazepam base and 57.7 mg mannitol per milliliter.

5 mL vial – 100 mg/mL total (equivalent to 50 mg/mL tiletamine and 50 mg/mL zolazepam) when reconstituted.

Approved by FDA under ANADA # 200-618

Manufactured in France for Virbac AH, Inc.
P.O. Box 162059, Fort Worth, TX, 76161
1-800-338-3659

Rev. 07/2024
71805-08

You Can Make a Difference for Pets Everywhere

OUR GOAL IS TO HELP ENSURE THAT **ALL PETS** GET THE CARE AND PROTECTION THEY DESERVE

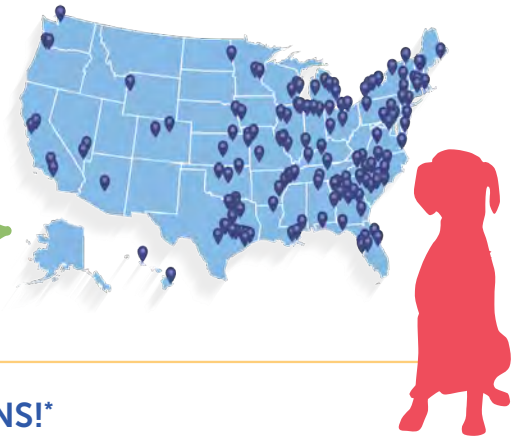
The Every Pet Project from Virbac donates

$2,500 X 2 pet charities X every month

SO FAR WE'VE DONATED MORE THAN

$415,000

TO 164 ANIMAL CHARITIES. IN 43 STATES.*



WITH OVER 109,331 NOMINATIONS!*

Scan this QR code

OR VISIT us.virbac.com/everypetproject

You nominate. We donate.

30 secs

It takes just 30 seconds to nominate your favorite animal charity, and you can nominate them **DAILY** to increase their chances of getting the donation.

THE MORE the Furrier!

Thank you for helping us to help more pets!

*Through December 2024

April 2025

Virbac

Shaping the future of animal health