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How to help owners safely regain control of their **AGGRESSIVE**, **FEARFUL**, **UNRULY** dogs on walks. p15

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Parasitic concerns: Mind the gap!

New research from CAPC compares veterinarians' and pet owners' concerns about various parasites.

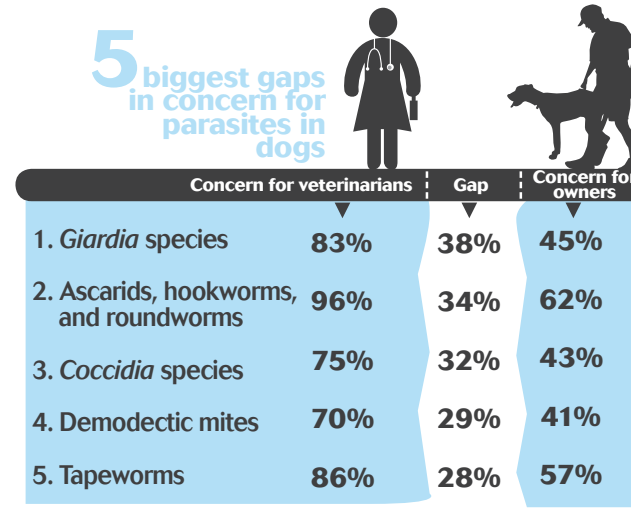
By Mindy Valcarcel, Editor

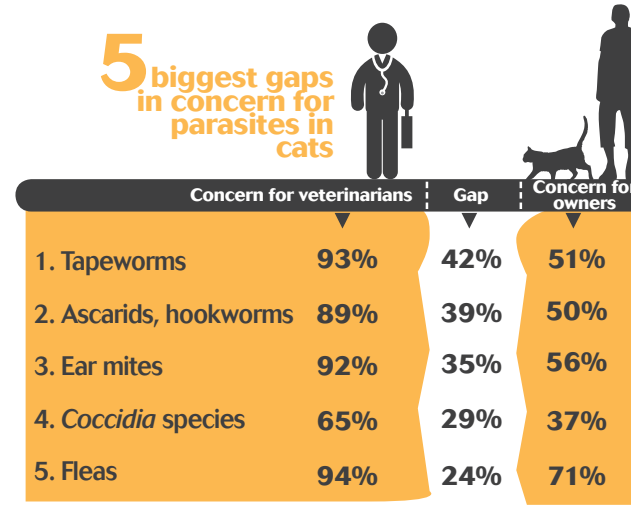
In 2014, in an effort called Connecting with Today's Clients, the Companion Animal Parasite Council (CAPC), supported by Bayer HealthCare, surveyed U.S. veterinarians, veterinary team members, and pet owners to gain some insight into whether all groups are on the same page when it comes to parasite control.

They interviewed 401 practicing veterinarians and 263 veterinary team members who work at least 30 hours a week in practices that see 75% or more small animals in a nonemergency setting. They also interviewed 2,000 dog or cat owners who had taken their pets to a veterinarian within the past two years.

Here is a sneak peek showing the level of concern veterinarians have about various parasites versus the level of concern of veterinary owners.

What does this mean? It signals a need for better communication with clients about parasite control and concerns in your area. At **dvm360.com /CAPCstudy**, we have resources ready for you, as well as more of this study's findings from us and our sister publications—*dvm360* magazine, *Veterinary Economics*, and *Firstline*. VM





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A **teratoma** in a turkey's eye

By Magdalena Szweda, DVM

A 6-week-old male turkey was presented for evaluation of an excrescence the size of a tennis ball (diameter 8 cm) in the area of the left eye (*Figure 1*). The results of a complete blood count showed evidence of infection (elevated WBC count = 49.5 x 10^9/L; reference range = 1.7 to 7.5 x 10^9/L). No abnormalities were found on a serum chemistry profile. Radiographic examination of the head showed that the tumor mass was loosely attached to the sclera but did not penetrate inside the eyeball.

After two days of clinical observation and therapy, enucleation was performed to remove the excrescence (*Figure 2*). Keep in mind that birds, unlike mammals, have relatively short optic nerves, so exaggerated traction on the globe can result in damage to the contralateral optic nerve, causing blindness in the contralateral eye. Birds have scleral ossicles, which can inhibit enucleation.[1,2]

>>>1. A 6-week-old male turkey with an excrescence the size of a tennis ball in the area of its left eye.

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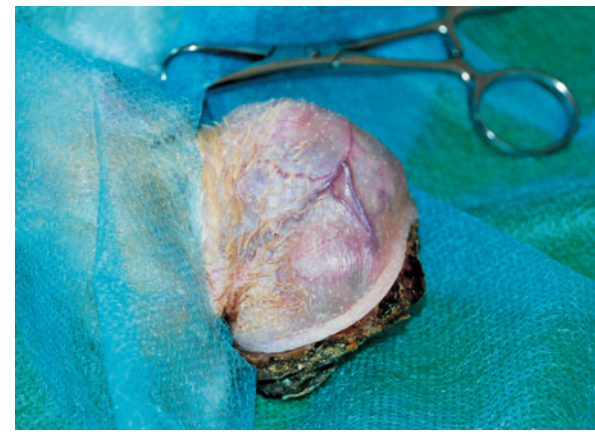

>>>2. A preoperative photo of the tumor mass loosely attached to the sclera.

The cornea was incised and the lens and vitreous were extruded to allow the globe to be collapsed. Intrasurgical observation revealed that the excrescence was a tumor attached to the eyeball. All the lacrimal tissue, the globe, and the eyelid margins were excised.

After excision, the skin was sutured routinely with a gauze swab inside the empty orbit. The swab was changed every day during the 14 days of convalescence. Some surgeons prefer to use an ocular prosthesis to prevent the sunken appearance characteristic of avian enucleation.[1] After surgery, the turkey received enrofloxacin (10 mg/kg intramuscularly) for 14 days and celecoxib (10 mg/kg orally) for five days. The sutures were removed 14 days after the enucleation (*Figure 3*).

>>>3. The patient 14 days after surgery, before removal of the sutures.

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Histopathologic examination

Microscopically, the tumor was composed of glandular structures similar to the intestine, ciliated epithelium resembling that of the respiratory system, and hyaline cartilage that formed various sizes of islands scattered throughout the tumor mass. There were also areas of the embryonal hyaline cartilage and endochondral ossification. The ossicles in the avian sclera were focally hyperplastic. All the tissues comprising the tumor were mature. Based on these findings, a teratoma was diagnosed.

Discussion

Teratomas arise from totipotential germ cells and can give rise to two or more embryonic layers (endoderm, mesoderm, ectoderm) with different types of tissues being present.[3] These tumors are not of uniform histologic structure but are a mixture of various randomly intermingled tissues. The exact mechanism of development of teratomas is still unclear. Teratomas are classified as immature (the tissue is not fully mature histologically; malignant) or mature (comprised of mature, fully differentiated tissues; benign).[4]

In this case, histopathologic examination together with the bird's young age suggested that the tumor could be congenital. The head surface location of the teratoma is rarely described in avian species.[5-8] The most common locations in birds are the ovary, testicle, and coelom.[9-11] VM

Teratomas are not of uniform histologic structure but are a mixture of various randomly intermingled tissues.

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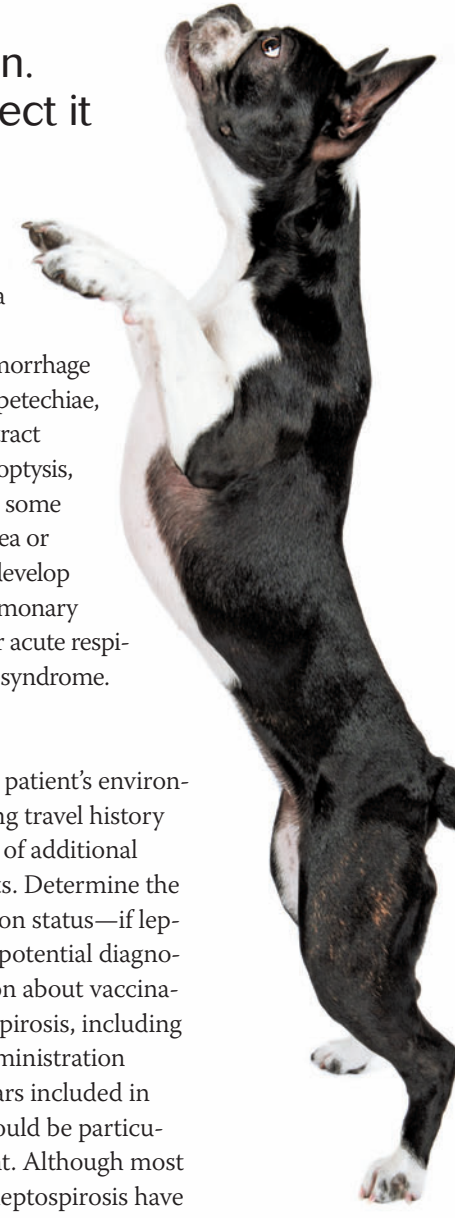
Canine leptospirosis: When to **suspect** it, how to **manage** it

You know that leptospirosis can be a chameleon. Here's a review to help you know when to suspect it and what to do about it.

By Mary Bowles, DVM, DACVIM



The dog is the primary companion animal in the United States affected by *Leptospira* species infection and can experience illness that ranges from mild to severe. The risk of infection has been shown to be greater for intact male, outdoor, working dogs, but dogs of any age, breed, or sex can become infected. Even dogs that live predominantly in the house can become infected—wild animals act as reservoirs for some serovars, and increasing encroachment on wildlife habitats by people increases the likelihood of interaction between pets and wildlife.

Although transmission can occur through bite wounds from infected animals, most dogs acquire infection when their mucous membranes or abraded skin comes into contact with soil, food, water, or other materials contaminated by urine from *Leptospira* species-infected domestic or wild animals.

Clinical signs

Clinical signs seen with leptospirosis can be mild or severe. Although general manifestations of illness such as fever and malaise may be present, signs related to the acute development of renal failure or hepatopathy should raise your index of suspicion for leptospirosis. Manifestations of acute renal failure frequently include polyuria/polydipsia (PU/PD) or oliguria/anuria, gastrointestinal (GI) signs, and abdominal pain. PU/PD can also be seen without renal failure and may be a consequence of acquired nephrogenic diabetes insipidus. Manifestations of hepatopathy often include GI signs, icterus, and bilirubinuria.

Be sure to perform an ophthalmologic evaluation since conjunctivitis and uveitis can be identified in some patients. Reluctance to move related to muscle pain may be present. Also be aware that vasculitis can occur, producing peripheral edema or cavitary effusion and hemorrhage manifested as petechiae, GI or urinary tract bleeding, hemoptysis, or epistaxis. In some cases, tachypnea or dyspnea may develop because of pulmonary hemorrhage or acute respiratory distress syndrome.

History

Ask about the patient's environment, including travel history and the status of additional household pets. Determine the pet's vaccination status—if leptospirosis is a potential diagnosis, information about vaccination for leptospirosis, including the date of administration and the serovars included in the vaccine, could be particularly important. Although most patients with leptospirosis have

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a history and clinical findings compatible with acute disease, leptospirosis should also be considered as an underlying cause in patients with chronic renal and hepatic disease.

Laboratory findings

The most common clinicopathologic abnormalities identified in patients with leptospirosis are related to acute kidney and liver injury. Azotemia has been reported in ≥ 80% of affected dogs in multiple regions of the United States and Canada.[1] Elevated liver enzyme activities and bilirubinemia frequently accompany azotemia—a combination of abnormalities that should prompt you to move leptospirosis higher on your list of differential diagnoses that should also include toxicoses, neoplasia, hypoadrenocorticism, and other infectious diseases such as systemic mycoses.

Evidence of renal failure is further supported by the frequent findings of hyperphosphatemia and isosthenuria along with the possible findings of hyposthenuria, glucosuria, proteinuria, and cylindruria. Multiple electrolyte abnormalities may be present, particularly hypokalemia. However, hyperkalemia can be found if the patient develops oliguria or anuria.

One of the most common complete blood count (CBC) findings is thrombocytopenia. Neutrophilia with or without a left shift and anemia may also be identified. The anemia is generally mildly to moderately nonregenerative but occasionally can be severe and regenerative in instances in which GI or pulmonary hemorrhage has occurred. In addition to thrombocytopenia, other coagulation profile abnormalities may be found such as increases in fibrin degradation products, D-dimer, prothrombin time, and partial thromboplasin time values, especially if disseminated intravascular coagulopathy becomes a complication.

Imaging and histologic examination

Imaging and histopathology can be considered as additional diagnostic procedures in cases of suspected leptospirosis. Renal ultrasonographic findings compatible with *Leptospira* species infection include bilateral renal enlargement, increased renal echogenicity that sometimes includes a more distinct band in the medullary area, and perirenal fluid. Thoracic radiography frequently reveals diffuse lung changes that can include an interstitial or alveolar pattern.

Renal and hepatic histologic findings in leptospirosis typically include varying degrees of renal interstitial nephritis, renal tubular necrosis, neutrophilic periportal hepatitis, and hepatic necrosis. *Leptospira* species organisms can sometimes be identified in tissue by using special stains (*e.g.* silver, peroxidase).

Specialized tests

MAT. The most common diagnostic test performed in patients suspected of having leptospirosis is the microscopic agglutination test (MAT), which uses patient sera and multiple serovars to detect antibody formation in acute and convalescent phases of illness. The highest serum dilution causing 50% agglutination of the organisms for each serovar tested is reported. False negative results can occur if the infecting serovar has not been included in the serovars tested. This possibility will be decreased if the laboratory selected for testing uses serovars more commonly found in the region from which the patient sample originated.

For a variety of reasons, it has been difficult to establish a precise titer level indicating definitive infection with a particular serovar. However, a single titer > 800 is highly suggestive of infection with the leptospire being tested, especially if compatible clinical signs are present and no recent vaccination for leptospirosis has occurred. Cross-reactivity can occur among serovars and lower titers, depending on the time of vaccination, are often present for serovars included

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Leptospirosis in cats

Although leptospirosis appears to be primarily a disease in dogs in the household pet population, cats can be infected but have been thought to experience mild manifestations of disease. *Leptospira canicola*, *pomona*, and *grippotyphosa* have been isolated from cats. Leptospires have been identified in the blood and urine of experimentally infected cats along with evidence of renal and hepatic inflammation.

Results from a recent Canadian study looking at *Leptospira* species in healthy cats and cats with kidney disease suggested that *Leptospira* organisms may play a role in the development of acute and chronic kidney disease in cats and that cats may play a role in transmission of these organisms through urine shedding.[1] In endemic areas, leptospirosis should be a consideration in cats with evidence of renal or hepatic disease or nonspecific illness. Doxycycline therapy may be an effective means of treating cats with leptospirosis.

Reference

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in the vaccine. MAT results can be negative in the acute phase of illness, so obtaining convalescent titers about two to four weeks after acute phase testing is advisable. Remember when evaluating acute and convalesent titers that a fourfold increase or decrease in *Leptospira* species serovar titer is considered indicative of recent infection.

PCR and culture. Leptospirosis can also be diagnosed by polymerase chain reaction (PCR) and culture methods. These methods can be especially useful in acute phase patients with negative or questionable MAT results that have not yet received antimicrobial therapy and patients with chronic renal or hepatic disease. Although blood is usually the sample of choice for PCR and culture techniques, a urine sample is often a better choice later in the course of disease when organisms reach a higher concentration in the urine.

Although culture can be a more accurate way of serotyping *Leptospira* species organisms, this diagnostic procedure requires aseptic sample collection, special culture media and handling, and three to six months for growth and identification of leptospires. PCR testing will identify *Leptospira* nucleic acid but not necessarily the specific serovar. Both false positive and negative results can occur with PCR testing, making concurrent acute and convalescent titer evaluation desirable.

Treatment

If leptospirosis is a reasonable differential diagnosis, initiate appropriate therapy immediately without waiting for confirmation of the diagnosis. Hospitalization is generally needed for adequate treatment. Therapy most commonly encompasses specific therapy for the *Leptospira* species organism as well as supportive care for acute renal failure and, in some cases, hepatic damage.

Keep in mind that leptospirosis is a zoonotic disease and that appropriate measures should be taken to prevent disease transmission through disinfection and protected handling of both the patient and waste materials. In addition, treatment of other dogs in the patient's household with a two-week course of doxycycline is recommended.

Prognosis

The prognosis for most patients is favorable for recovery with appropriate medical care. Discharge from the hospital setting can occur after tapering fluid therapy and when the patient is stable, is not showing serious outward clinical signs of illness, has normal or consistently improved laboratory values, and is able to adequately eat and drink. Azotemia may not completely resolve for weeks. Occasionally, patients will sustain permanent impairment of kidney function.

Recognition of which serovar is most likely responsible for infection of the patient will help identify environmental risk factors for reinfection and infection of additional dogs in the household. Annual vaccination of the recovered patient with a four-serovar vaccine starting one year after recovery is currently recommended.[2] VM

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A better walk:

Training dogs **NOT** to *lunge*, *growl*, and *pull* on a leash

New Year's resolutions often involve getting more exercise—and this includes dogs as well. But reactivity on a leash is a common problem, making it less likely for owners to venture out with their dogs. This step-by-step training plan will help you help owners take control and enjoy walking their dogs again. *By Wayne Hunthausen, DVM*

Ms. G's dog, Tommy, was slowly becoming grossly overweight. He weighed 10 lb more than the last time I saw him and at least 20 lb more than he should weigh. "Tommy needs to pass on the midnight snacks," I told her, "but just as important, he needs to be getting more exercise."

Ms. G appeared distressed as well as concerned. "I know he needs more exercise," she said, "and I want to get him out more. But he's a big boy and I just can't control him when I walk him on a leash. He constantly barks and lunges

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at everything he sees. It's so embarrassing!"

Ms. G is not alone in her dilemma. Reactivity on a leash is a common canine behavior problem and is often stressful for owners. It can be caused by a variety of underlying problems, including aggression, fear, unruliness, play-soliciting behavior, or inadequate training. The problem can usually be successfully treated if the owners have the commitment, tools, and correct information to get the job done. Outlined below is a typical plan that I use to address this problem.

Training overview

The purpose of these exercises is to give owners more control over their dogs on walks and to replace lunging, barking, or aggressive or fearful behaviors with calm, quiet, and relaxed behaviors. Training at a distance beyond the response threshold (*see "Response threshold distances" below*) is absolutely necessary. Dogs are less manageable and have difficulty learning when they are highly aroused.

Owners need to stay as relaxed as possible and think of these exercises as games to play with their dogs. If aggression is part of a dog's reactive behavior, the person walking the dog is responsible for others' safety and must ensure that leashes and halters are secure and that there is no opportunity for physical contact with other dogs or people.

If aggression is part of a dog's reactive behavior, the person walking the dog is responsible for others' safety and must ensure that leashes and halters are secure and that there is no opportunity for physical contact with other dogs or people.

Preparation

Before the social conditioning process begins, the dog must be taught to dependably come, sit, stay, and heel on a leash. This training may require the help of a private trainer since these dogs usually do poorly in a class situation. It should be noted that throughout the entire training process, only positive reinforcement types of training techniques should be used.

Next, owners need to teach their dogs that they are in control. By setting boundaries, the owner will obtain better compliance and dependability from obedience cues. This can be accomplished by initiating a social structure or a nothing-in-life-is-free program.

As part of this program, the owner should request that the dog sit before getting anything it wants or needs, the dog should be ignored when it demands attention, and the dog should frequently be asked to stay before being allowed to follow owners around the home or yard or before going in or out of the home. During training, all commands should be given in an upbeat and relaxed tone of voice.

Tools

In addition to having a social conditioning plan (*see "Phase 1: Counterconditioning at a distance" below to begin the training plan*), other tools that owners will need when training their dogs against reactive behaviors are positive reinforcers and instruments for maintaining physical control (*e.g.* an appropriate leash, a head halter).

Reinforcers. Owners must determine their dogs' most desirable food (*e.g.* very tasty

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See brief summary on page 18

RP141006

dog treats, freeze-dried liver, cooked chicken or turkey, cheese, fat-free turkey hot dogs) and give that food only during the dogs' social and obedience conditioning training. It is helpful to always say a specific word or phrase, such as "good dog," as the food is given. By frequently associating specific words with food, the words can be used as relatively strong reinforcers even when food is not present.

Physical control. To maintain physical control of dogs during training, owners should keep their dogs on 4- to 6-ft leashes. Owners should have one hand in the loop, and the other hand should be holding the leash a few feet from the collar. Retractable leashes are unreliable and unwieldy and should not be used. Devices that cause discomfort—such as pinch collars, shock collars, and choke collars—should be avoided because owners want their dogs to develop positive associations with people or other dogs they react toward and avoid unpleasant associations. Leash corrections or leash pops are not appropriate.

If more control is needed, the dog should be trained to wear a head halter. Owners may also consider a basket muzzle if there is any chance an aggressive dog might inadvertently have contact with another person or dog.

Response threshold distances

There are two threshold distances of concern: orienting threshold distance and reactive threshold distance. Training takes place between the two threshold distances.

The orienting threshold distance is the distance at which the dog barely recognizes and begins to focus toward the trigger stimulus (*e.g.* dog, person, bike). This distance should be significantly farther than the distance at which the owner begins to lose control of the dog.

The reactive threshold distance is the distance at which the dog begins to exhibit the unwanted behaviors (*e.g.* barking, growling, lunging). This distance may vary depending on the stimulus. For example, a dog that is aggressive to people might be reactive to most men at 100 ft but reactive to men with hats at 60 ft. Or a dog that is reactive to other dogs might react to large dogs at a farther distance than it does to small dogs.

Training away from the neighborhood

Social conditioning training does not always have to take place on neighborhood sidewalks, and it can be beneficial to work in a wide variety of environments. In some areas, especially those where the neighborhood environment is congested or busy, it may be helpful to actually begin away from home. Owners can perform the training exercises wherever there might be a trigger stimulus. Here are some instructions to give owners when implementing this training in other environments.

Walking trails

- Take a position in an open area near the trail at the orienting threshold distance.
- Ask the dog to sit or stay for a treat whenever it sees a trigger stimulus.
- Gradually move closer to the trail.

Malls

- Train dogs during quiet times of the day.
- Take a position along the edge of the parking lot at the orienting threshold distance.
- Ask the dog to sit or stay for a treat whenever it sees a trigger stimulus step out of a car or walk out of the mall toward the dog.
- Gradually move closer, but not into the mall.

Phase 1: Counterconditioning at a distance

Owners should begin by walking their dogs in relatively quiet spots where trigger stimuli appear intermittently. (*See the sidebar "Training away from the neighborhood."*) Crowded areas should be avoided. Varying the time of the walk can be helpful, but owners should make sure it is at a time when there is a low density of people or dogs. Owners should be careful to keep their dogs beyond the reactive threshold distance.

When a dog orients toward a stimulus, the owner should immediately say the dog's name in an upbeat tone and present a treat at the same time. The owner should request the dog sit or stay for no more than two seconds, give the treat, and say, "good dog." The owner and dog should then continue slowly walking ahead. When the dog orients toward the stimulus again, the sequence should be repeated.

Before the stimulus crosses the second threshold distance (reactive threshold distance) and the dog becomes reactive, the owner should turn with the dog and walk in the opposite direction or down a side street. Over time, the dog should gradually be allowed to get closer to the stimulus before changing direction. (Hint: The dog is getting close to its personal reactive threshold if it takes the treat slowly or overly rough or fast, is slow to sit, whines, yawns, or maintains a strong focus on the stimulus even while taking the food.)

Phase 2: Passing by across the street

Once the dog will consistently perform a relaxed sit or stay about 40 ft from the stimulus, the next step is to continue to walk straight ahead but across the street from the stimulus as the stimulus passes in the opposite direction. The owner should request the dog sit or stay for treats several times as he or she walks the dog in the direction of the stimulus. When about 40 ft from the stimulus, the owner should place a large treat in front the dog's nose, repeatedly say "heel" in an excited and upbeat tone, and briskly walk forward, keeping the dog

The ABCs of treating reactive behaviors

Help owners treat their dog's reactive behaviors—whether the dog is exhibiting aggression, fear, or unruly behavior—by recommending they follow these ABCs.

Avoidance

Owners should manage their dogs and the environment so that the dogs have little or no opportunity to perform the undesirable behaviors. Avoidance keeps situations safe and prevents the problem from worsening.

Behavioral control

Owners should review obedience training, set social boundaries, and institute a nothing-in-life-is-free program to maintain more control over an aggressive or unruly dog. Putting the owners in control takes the weight off the shoulders of the fearful dog because it learns its owners control social situations and it does not need to assert control.

Condition desirable behavior

Replace problem behaviors with acceptable behaviors by using desensitization, counterconditioning, and operant training methods that emphasize positive methods and avoid aversive ones.

Desensitization. The process of diminishing responsiveness to a stimulus through repeated exposure to it at a low enough level that no or minimal response is seen.

Counterconditioning. The replacement of an unwanted behavior or response to a stimulus with a desirable behavior or response by associating something positive with the stimulus.

Operant conditioning. A method of learning that occurs through rewards and punishments for a behavior. Through these rewards and punishments, an association is made between a behavior and a consequence for that behavior, causing the behavior to either increase or decrease in frequency. It is sometimes referred to as *instrumental conditioning*.

Resources for these behavior modification techniques

- Bowen J, Heath S. Learning theory and behaviour modification. In: *Behaviour problems in small animals*. Edinburgh, Scotland: Elsevier, 2005;37-48.
- Lindsay SR. *Handbook of applied dog behavior and training*. Vol. 1-3. Ames, Iowa: Iowa State University Press, 2000, 2001, 2005.
- Mills DS. Training and learning protocols. In: Horwitz DF, Mills DS, ed. *BSAVA manual of canine and feline behavioural medicine*. 2nd ed. Gloucester, UK: BSAVA, 2009;49–64.
- Pryor K. *Don't shoot the dog. The new art of dog training*. Gloucester: Ringpress, 2002.
- Pryor K. *Reaching the animal mind: clicker training and what it teaches us about all animals*. New York: Scribner, 2009.
- Reid P. *Excel-erated leaning. Explaining in plain English how dogs learn and how best to teach them*. Oakland, California: James and Kenneth Publishers, 1996.

oriented toward the food and its nose pointing straight ahead.

Phase 3: Sitting or staying beside the sidewalk

When the dog consistently ignores the stimulus across the street, the owner can proceed to Phase 3. As the stimulus approaches directly toward the dog from the front, the dog is commanded to sit or stay at a position about 20 ft to the side of the sidewalk. A treat is held in front of the dog's nose until the stimulus passes, and then the dog is given the treat and released. An alternative approach for a dog that might have difficulty maintaining a long stay would be to have the owner give a series of sit or stay cues for treats as the stimulus passes. Slowly and gradually, the dog moves closer to the sidewalk during subsequent passes.

Other considerations

No scolding. Owners should avoid scolding dogs or saying, "leave it," "watch me," or "look at me," in tense or agitated tones as a stimulus approaches. These types of responses will typically increase a dog's arousal and reactivity. Owners should maintain safe control, stay beyond the reactive threshold distance, be calm but firm, and try to keep the leash as loose as possible.

Exhibiting reactive behavior. If a dog exhibits a reactive behavior (lunging, barking, growling) during a walk, the owner should immediately turn and briskly walk or jog out of the situation. The owner should be firm and calm and not yell, scold, give a leash correction, or punish the dog.

Stranger petting. If a dog has a history of aggression or a strong fear response and someone asks to pet the dog during a walk, the owner should decline. However, if the owner, the approaching person, and the dog are all relaxed, the owner can say, "I'm training this dog, so you can't pet him, but would you mind tossing treats to him when I ask him to sit?" and allow the person to toss a treat to the dog. If anyone, including the dog, is not relaxed, the owner should decline the request, maintain a safe distance, and walk away with the dog.

Territorial behavior. Allowing a dog to aggressively lunge, bark, or growl while standing at windows, fence lines, or on tie-downs in the yard will undo the training done on walks. The dog should not be given the opportunity to perform these behaviors. Preventing or blocking access to window, doors, and fences can prevent this behavior. If this is not possible and the reactive behavior occurs, it should be interrupted. That can be done by having the owner use novel, loud noises that are appropriate for the dog's temperament (*e.g.* a shake can, a hiker's emergency whistle, InteroSTOP—Meridian Animal Health, an air horn) or by having the dog wear a citronella spray antibark collar. Shock collars should be avoided.

Once the dog stops the unacceptable behavior, it can be redirected to another acceptable behavior. The owner should always reward the dog with praise or a treat if the dog notices dogs, people, or other stimuli passing by the home and does not react.

Medication. Drugs may be necessary for dogs with unstable temperaments or for dogs in situations in which it is difficult or impossible to stay beyond the reactive threshold distance (*e.g.* dogs with extremely long reactive threshold distances, dogs that live in condominiums or apartment complexes, dogs that must be walked in crowded urban areas).

If medication is needed, I usually prescribe a selective serotonin reuptake inhibitor (SSRI). Owners can give fluoxetine, paroxetine, or sertraline to their dogs at 0.5 to 2 mg/kg once a day.

Since SSRIs can take up to six weeks to become effective, I often recommend that owners give dogs a second medication as needed to reduce arousal. For those situations, clonidine (0.01 to 0.05 mg/kg b.i.d.) or trazodone (2 or 3 mg/kg q.i.d.) given about an hour before walks can be helpful. Start at a low dosage and increase to effect.

Trazodone has an effect on the serotonin system, so lower dosages may be required for effect and to avoid serotonin syndrome, a serious and potentially fatal condition that may arise when antidepressants that inhibit serotonin reuptake are given at high doses or in combination with other drugs and dietary supplements that may increase serotonin. The serotonin syndrome results mainly in neurologic, autonomic, and gastrointestinal signs, including restlessness, mental confusion, hyperesthesia, shivering, shaking, hyperthermia, tachycardia, tachypnea, abdominal pain, diarrhea, vomiting, hypersalivation, twitching, tremors, seizures, coma, and death.

Pretreatment and follow-up diagnostic tests should be considered depending on the age and health of the dog, the type of medication given, and if multiple drugs are being administered concurrently.

Attempting to rush the dog through the treatment stages may actually delay progress and can be dangerous if aggression is involved.

The duration of training required to resolve this type of problem depends on the pet's temperament, the duration of the problem, the severity of the problem, and the expertise and time dedicated by the owner. Training may take several weeks to many months. The owner needs to understand this and that patience is very important. Attempting to rush the dog through the treatment stages may actually delay progress and can be dangerous if aggression is involved. Encouragement and timely follow-ups or progress reports from the owner can be essential for accomplishing a satisfactory, safe outcome. VM

Suggested Reading

1. Bain M. Aggression toward unfamiliar people and animals. In: Horwitz DF, Mills DS, eds. *BSAVA manual of canine and feline behavioural medicine*. 2nd ed. Gloucester, UK: BSAVA, 2009;211-222.
2. Haug LI. Canine aggression toward unfamiliar people and dogs. *Vet Clin North Am Small Anim Pract* 2008;38:1023-1041.
3. Landsberg GL, Hunthausen WL, Ackerman L. *Handbook of behavior problems of the dog and cat*. 3rd ed. Philadelphia, Pa: Saunders, 2013;95-112, 134, 181-210, 297-326.

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090340591/0

NADA 141-273, Approved by FDA

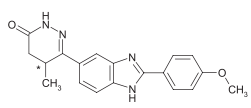
Vetmedin®

(pimobendan)
Chewable Tablets

Cardiac 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: Vetmedin (pimobendan) is supplied as oblong half-scored chewable tablets containing 1.25, 2.5, 5 or 10 mg pimobendan per tablet. Pimobendan, a benzimidazole-pyridazinone derivative, is a non-sympathomimetic, non-glycoside inotropic drug with vasodilatative properties. Pimobendan exerts a stimulatory myocardial effect by a dual mechanism of action consisting of an increase in calcium sensitivity of cardiac myofilaments and inhibition of phosphodiesterase (Type III). Pimobendan exhibits vasodilating activity by inhibiting phosphodiesterase III activity. The chemical name of pimobendan is 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazole-5-yl]-5-methyl-3(2H)-pyridazinone. The structural formula of pimobendan is:



Indications: Vetmedin (pimobendan) is indicated for the management of the signs of mild, moderate, or severe (modified NYHA Class II[a], III[b], or IV[c]) congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI) or dilated cardiomyopathy (DCM). Vetmedin is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

[a] A dog with modified New York Heart Association (NYHA) Class II heart failure has fatigue, shortness of breath, coughing, etc. apparent when ordinary exercise is exceeded.

[b] A dog with modified NYHA Class III heart failure is comfortable at rest, but exercise capacity is minimal.

[c] A dog with modified NYHA Class IV heart failure has no capacity for exercise and disabling clinical signs are present even at rest.

Dosage and Administration: Vetmedin should be administered orally at a total daily dose of 0.23 mg/lb (0.5 mg/kg) body weight, using a suitable combination of whole or half tablets. The total daily dose should be divided into 2 portions that are not necessarily equal, and the portions should be administered approximately 12 hours apart (i.e., morning and evening). The tablets are scored and the calculated dosage should be provided to the nearest half tablet increment.

Contraindications: Vetmedin should not be given in cases of hypertrophic cardiomyopathy, aortic stenosis, or any other clinical condition where an augmentation of cardiac output is inappropriate for functional or anatomical reasons.

Warnings: Only for use in dogs with clinical evidence of heart failure. At 3 and 5 times the recommended dosage, administered over a 6-month period of time, pimobendan caused an exaggerated hemodynamic response in the normal dog heart, which was associated with cardiac pathology (See **Animal Safety**).

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

Precautions: The safety of Vetmedin has not been established in dogs with asymptomatic heart disease or in heart failure caused by etiologies other than AVVI or DCM. The safe use of Vetmedin has not been evaluated in dogs younger than 6 months of age, dogs with congenital heart defects, dogs with diabetes mellitus or other serious metabolic diseases, dogs used for breeding, or pregnant or lactating bitches.

Adverse Reactions: Clinical findings/adverse reactions were recorded in a 56-day field study of dogs with congestive heart failure (CHF) due to AVVI (256 dogs) or DCM (99 dogs). Dogs were treated with either Vetmedin (175 dogs) or the active control enalapril maleate (180 dogs). Dogs in both treatment groups received additional background cardiac therapy (See **Effectiveness** for details and the difference in digoxin administration between treatment groups).

The Vetmedin group had the following prevalence (percent of dogs with at least one occurrence) of common adverse reactions/new clinical findings (not present in a dog prior to beginning study treatments): poor appetite (38%), lethargy (33%), diarrhea (30%), dyspnea (29%), azotemia (14%), weakness and ataxia (13%), pleural effusion (10%), syncope (9%), cough (7%), sudden death (6%), ascites (6%), and heart murmur (3%). Prevalence was similar in the active control group. The prevalence of renal failure was higher in the active control group (4%) compared to the Vetmedin group (1%).

Adverse reactions/new clinical findings were seen in both treatment groups and were potentially related to CHF, the therapy of CHF, or both. The following adverse reactions/new clinical findings are listed according to body system and are not in order of prevalence: CHF death, sudden death, chordae tendineae rupture, left atrial tear, arrhythmias overall, tachycardia, syncope, weak pulses, irregular pulses, increased pulmonary edema, dyspnea, increased respiratory rate, coughing, gagging, pleural effusion, ascites, hepatic congestion, decreased appetite, vomiting, diarrhea, melena, weight loss, lethargy, depression, weakness, collapse, shaking, trembling, ataxia, seizures, restlessness, agitation, pruritus, increased water consumption, increased urination, urinary accidents, azotemia, dehydration, abnormal serum electrolyte, protein, and glucose values, mild increases in serum hepatic enzyme levels, and mildly decreased platelet counts.

See Table 1 for mortality due to CHF (including euthanasia, natural death, and sudden death) and for the development of new arrhythmias (not present in a dog prior to beginning study treatments) by treatment group and type of heart disease (AVVI or DCM) in the 56-day field study.

Table 1: CHF Death and New Arrhythmias in the 56-Day Field Study

	Vetmedin® Group	Active Control Group
Dogs that died due to CHF	14.3% n = 175	14.4% n = 180
	9 of 126 dogs with AVVI	16 of 130 dogs with AVVI
	16 of 49 dogs with DCM	10 of 50 dogs with DCM
Dogs that developed new arrhythmias[a]	39.4% n = 175	45.0% n = 180
	45 of 126 dogs with AVVI	59 of 130 dogs with AVVI
	24 of 49 dogs with DCM	22 of 50 dogs with DCM

[a] New arrhythmias included supraventricular premature beats and tachycardia, atrial fibrillation, atrioventricular block, sinus bradycardia, ventricular premature beats and tachycardia, and bundle branch block

Following the 56-day masked field study, 137 dogs in the Vetmedin group were allowed to continue on Vetmedin in an open-label extended-use study without restrictions on concurrent therapy. The adverse reactions/new clinical findings in the extended-use study were consistent with those reported in the 56-day study, with the following exception: One dog in the extended-use study developed acute cholestatic liver failure after 140 days on Vetmedin and furosemide.

In foreign post-approval drug experience reporting, the following additional suspected adverse reactions were reported in dogs treated with a capsule formulation of pimobendan: hemorrhage, petechia, anemia, hyperactivity, excited behavior, erythema, rash, drooling, constipation, and diabetes mellitus.

To report suspected adverse reactions, to obtain a Material Safety Data Sheet, or for technical assistance call 1-866-638-2226.

Clinical Pharmacology: Pimobendan is oxidatively demethylated to a pharmacologically active metabolite which is then conjugated with sulfate or glucuronic acid and excreted mainly via feces. The mean extent of protein binding of pimobendan and the active metabolite in dog plasma is >90%. Following a single oral administration of 0.25 mg/kg Vetmedin tablets the maximal mean (± 1 SD) plasma concentrations (Cmax) of pimobendan and the active metabolite were 3.09 (0.76) ng/ml and 3.66 (1.21) ng/ml, respectively. Individual dog Cmax values for pimobendan and the active metabolite were observed 1 to 4 hours post-dose (mean: 2 and 3 hours, respectively). The total body clearance of pimobendan was approximately 90 mL/min/kg, and the terminal elimination half-lives of pimobendan and the active metabolite were approximately 0.5 hours and 2 hours, respectively. Plasma levels of pimobendan and active metabolite were below quantifiable levels by 4 and 8 hours after oral administration, respectively. The steady-state volume of distribution of pimobendan is 2.6 L/kg indicating that the drug is readily distributed into tissues. Food decreased the bioavailability of an aqueous solution of pimobendan, but the effect of food on the absorption of pimobendan from Vetmedin tablets is unknown.

In normal dogs instrumented with left ventricular (LV) pressure transducers, pimobendan increased LV dP/dtmax (a measure of contractility of the heart) in a dose dependent manner between 0.1 and 0.5 mg/kg orally. The effect was still present 8 hours after dosing. There was a delay between peak blood levels of pimobendan and active metabolite and the maximum physiologic response (peak LV dP/dtmax). Blood levels of pimobendan and active metabolite began to drop before maximum contractility was seen. Repeated oral administration of pimobendan did not result in evidence of tachyphylaxis (decreased positive inotropic effect) or drug accumulation (increased positive inotropic effect). Laboratory studies indicate that the positive inotropic effect of pimobendan may be attenuated by the concurrent use of a β-adrenergic blocker or a calcium channel blocker.

Effectiveness: In a double-masked, multi-site, 56-day field study, 355 dogs with modified NYHA Class II, III, or IV CHF due to AVVI or DCM were randomly assigned to either the active control (enalapril maleate) or the Vetmedin (pimobendan) treatment group. Of the 355 dogs, 52% were male and 48% were female; 72% were diagnosed with AVVI and 28% were diagnosed with DCM; 34% had Class II, 47% had Class III, and 19% had Class IV CHF. Dogs ranged in age and weight from 1 to 17 years and 3.3 to 191 lb, respectively. The most common breeds were mixed breed, Doberman Pinscher, Cocker Spaniel, Miniature/Toy Poodle, Maltese, Chihuahua, Miniature Schnauzer, Dachshund, and Cavalier King Charles Spaniel. The 180 dogs (130 AVVI, 50 DCM) in the active control group received enalapril maleate (0.5 mg/kg once or twice daily), and all but 2 received furosemide. Per protocol, all dogs with DCM in the active control group received digoxin. The 175 dogs (126 AVVI, 49 DCM) in the Vetmedin group received pimobendan (0.5 mg/kg/day divided into 2 portions that were not necessarily equal, and the portions were administered approximately 12 hours apart), and all but 4 received furosemide. Digoxin was optional for treating supraventricular tachyarrhythmia in either treatment group, as was the addition of a β-adrenergic blocker if digoxin was ineffective in controlling heart rate. After initial treatment at the clinic on Day 1, dog owners were to administer the assigned product and concurrent medications for up to 56±4 days.

The determination of effectiveness (treatment success) for each case was based on improvement in at least 2 of the 3 following primary variables: modified NYHA classification, pulmonary edema score by a masked veterinary radiologist, and the investigator's overall clinical effectiveness score (based on physical examination, radiography, electrocardiography, and clinical pathology). Attitude, pleural effusion, coughing, activity level, furosemide dosage change, cardiac size, body weight, survival, and owner observations were secondary evaluations contributing information supportive to product effectiveness and safety. Based on protocol compliance and individual case integrity, 265 cases (134 Vetmedin, 131 active control) were evaluated for treatment success on Day 29. See Table 2 for effectiveness results.

Table 2: Effectiveness Results for the 56-Day Field Study

	Vetmedin® Group	Active Control Group
Treatment Success on Day 29	80.7% n=134	76.3% n=131
	88 of 101 dogs with AVVI	77 of 100 dogs with AVVI
	20 of 33 dogs with DCM	23 of 31 dogs with DCM
Treatment Success on Day 56	71.1% n=113	67.2% n=110
	66 of 85 dogs with AVVI	56 of 85 dogs with AVVI
	13 of 28 dogs with DCM	17 of 25 dogs with DCM
No increase in furosemide dose between Day 1 and Day 29	78.3% n=130	68.6% n=126

At the end of the 56-day study, dogs in the Vetmedin group were enrolled in an unmasked field study to monitor safety under extended use, without restrictions on concurrent medications.

Vetmedin was used safely in dogs concurrently receiving furosemide, digoxin, enalapril, atenolol, spironolactone, nitroglycerin, hydralazine, diltiazem, antiparasitic products (including heartworm prevention), antibiotics (metronidazole, cephalexin, amoxicillin-clavulanate, fluoroquinolones), topical ophthalmic and otic products, famotidine, theophylline, levothyroxine sodium, diphenhydramine, hydrocodone, metoclopramide, and butorphanol, and in dogs on sodium-restricted diets.

Palatability: In a laboratory study, the palatability of Vetmedin was evaluated in 20 adult female Beagle dogs offered doses twice daily for 14 days. Ninety percent (18 of 20 dogs) voluntarily consumed more than 70% of the 28 tablets offered. Including two dogs that consumed only 4 and 7% of the tablets offered, the average voluntary consumption was 84.2%.

Animal Safety: In a laboratory study, Vetmedin chewable tablets were administered to 6 healthy Beagles per treatment group at 0 (control), 1, 3, and 5 times the recommended dosage for 6 months. See Table 3 for cardiac pathology results. The cardiac pathology/histopathology noted in the 3X and 5X dose groups is typical of positive inotropic and vasodilator drug toxicity in normal dog hearts, and is associated with exaggerated hemodynamic responses to these drugs. None of the dogs developed signs of heart failure and there was no mortality.

Table 3: Incidence of Cardiac Pathology/ Histopathology in the Six-month Safety Study

Severe left ventricular hypertrophy with multifocal subendocardial ischemic lesions	One 3X and two 5X dogs[a]
Moderate to marked myxomatous thickening of the mitral valves	Three 5X dogs
Myxomatous thickening of the chordae tendineae	One 3X and two 5X dogs
Endocardial thickening of the left ventricular outflow tract	One 1X, two 3X, and two 5X dogs
Left atrial endocardial thickening (jet lesions) in 2 of the dogs that developed murmurs of mitral valve insufficiency	One 3X and one 5X dog
Granulomatous inflammatory lesion in the right atrial myocardium	One 3X dog

[a] Most of the gross and histopathologic findings occurred in these three dogs

Murmurs of mitral valve insufficiency were detected in one 3X (Day 65) and two 5X dogs (Days 135 and 163). These murmurs (grades II-III of VI) were not associated with clinical signs.

Indirect blood pressure was unaffected by Vetmedin at the label dose (1X). Mean diastolic blood pressure was decreased in the 3X group (74 mmHg) compared to the control group (82 mmHg). Mean systolic blood pressure was decreased in the 5X group (117 mmHg) compared to the control group (124 mmHg). None of the dogs had clinical signs of hypotension.

On 24-hour Holter monitoring, mean heart rate was increased in the 5X group (101 beats/min) compared to the control group (94 beats/min). Not counting escape beats, the 3X and 5X groups had slightly higher numbers of isolated ventricular ectopic complexes (VEs). The maximum number of non-escape VEs recorded either at baseline or in a control group dog was 4 VEs/24 hours. At either Week 4 or Week 20, three 3X group dogs had maximums of 33, 13, and 10 VEs/24 hours, and two 5X group dogs had maximums of 22 and 9 VEs/24 hours. One 1X group dog with no VEs at baseline had 6 VEs/24 hours at Week 4 and again at Week 20. Second-degree atrioventricular heart block was recorded in one 3X group dog at Weeks 4 and 20, and in one dog from each of the 1X and 5X groups at Week 20. None of the dogs had clinical signs associated with these electrocardiogram changes.

Treatment was associated with small differences in mean platelet counts (decreased in the 3X and 1X groups), potassium (increased in the 5X group), glucose (decreased in the 1X and 3X groups), and maximum blood glucose in glucose curves (increased in the 5X group). All individual values for these variables were within the normal range. Three 1X and one 5X group dogs had mild elevations of alkaline phosphatase (less than two times normal). Loose stools and vomiting were infrequent and self-limiting.

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

How Supplied:

Vetmedin® (pimobendan) Chewable Tablets:
Available as 1.25, 2.5, 5 and 10 mg oblong half-scored chewable tablets - 50 tablets per bottle.

NDC 0010-4480-01-1.25 mg - 50 tablets
NDC 0010-4481-01-2.5 mg - 50 tablets
NDC 0010-4482-01-5 mg - 50 tablets
NDC 0010-4479-01-10 mg - 50 tablets

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Julie McCreadie, LVT
Rochester, Michigan

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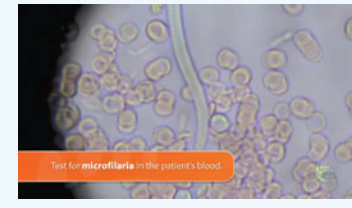

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DON'T WAIT.

Now VETMEDIN offers convenient dosing options for dogs of all sizes.

VETMEDIN is now available in four sizes:
1.25 mg, **2.5 mg**, 5 mg, and **10 mg**.

Busby, 12 lb
1.25 mg (2x day) OR half a 2.5 mg (2x day)*

Lucky, 22 lb
2.5 mg (2x day) OR half a 5 mg (2x day)*

Clyde, 65 lb
10 mg in morning and half a 10 mg in evening*

Simon, 120 lb
Two 10 mg in morning and one 10 mg in evening*

VETMEDIN is a well-established treatment for CHF caused by atrioventricular valvular insufficiency and dilated cardiomyopathy.[1,2] Now, no matter the size of the dog, our new dosing options can help you give owners convenient, cost-effective choices that help encourage compliance.

ACT NOW. Use VETMEDIN at the first clinical signs of CHF in dogs of any size or shape.

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(pimobendan) CHEWABLE TABLETS
A heart's best friend

IMPORTANT SAFETY INFORMATION: VETMEDIN should not be given in case of hypertrophic cardiomyopathy, aortic stenosis, or any other clinical condition where an augmentation of cardiac output is inappropriate for functional or anatomical reasons. The safety of VETMEDIN has not been established in dogs with asymptomatic heart disease or in heart failure caused by etiologies other than atrioventricular valvular insufficiency or dilated cardiomyopathy. Use only in dogs with clinical evidence of heart failure. The most common side effects reported in field studies were poor appetite, lethargy, diarrhea, dyspnea, azotemia, weakness, and ataxia. If side effects should occur, pet owners should contact their veterinarian. Please refer to the package insert for complete product information or visit **www.vetmedin.com**.

See brief summary on page 23

* All doses are provided as tablets.

References: 1. Häggström J, Boswood A, O'Grady M, et al. *J Vet Intern Med.* 2008;22(5):1124–1135.
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