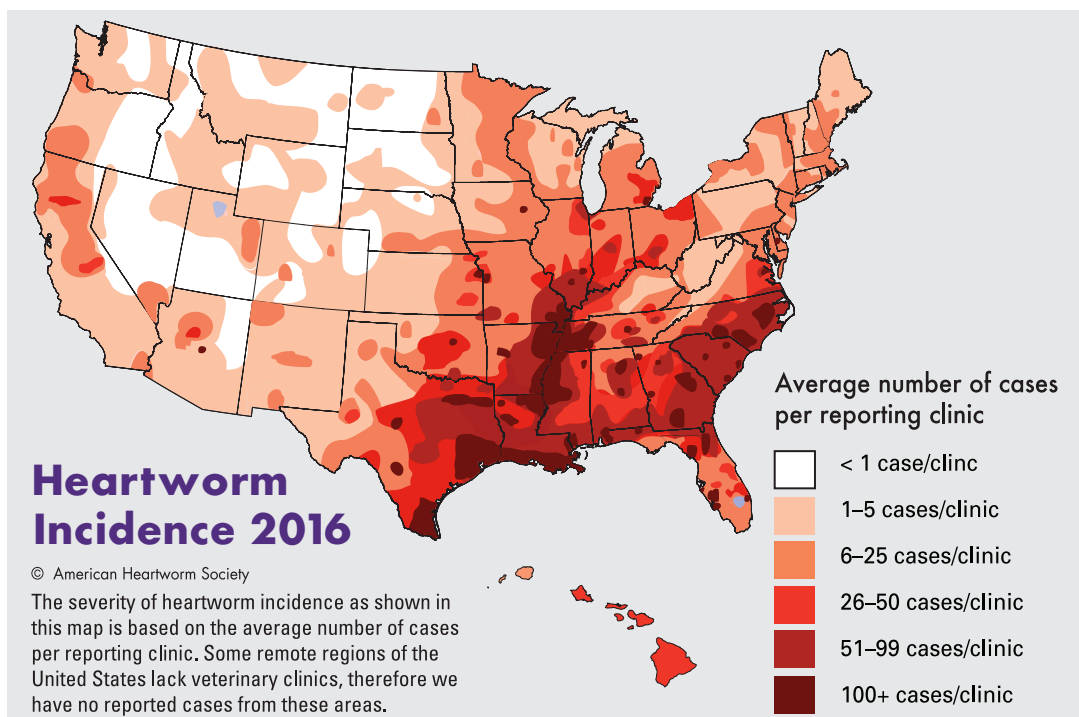




Interpreting the New 2016 AHS HEARTWORM INCIDENCE MAP

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Every three years, the AHS gathers data via an incidence survey and creates a map that shows the survey results. The latest AHS survey was conducted in January and February 2017 and focused on 2016 calendar-year heartworm testing, with more than 4,500 veterinary practices and shelters responding. The 2016 map was released in April for Heartworm Awareness Month. Since its release, AHS has received some comments about interpretation of the map so we asked AHS Ex-Officio Board Member Dr. Doug Carithers, who conducted the survey, to address those questions.

Since the first modern AHS heartworm map was produced in 2002 (on 2001 data), along with the AHS copyright, every AHS map has had the following explanation attached:

“The severity of heartworm incidence as shown in this map is based on the average number of cases per reporting clinic. Some remote regions of the United States lack veterinary clinics, therefore we have no reported cases from these areas.”

The reason for including this statement is to ensure transparency and clarity, and never to over-state the map.

■ INCIDENCE

The map is intended to show incidence, not prevalence. *Incidence* is defined as the number of new cases identified in a specific time frame; thus, the request in the survey for cases identified in the previous calendar year. (*Prevalence*

Continues on page 7



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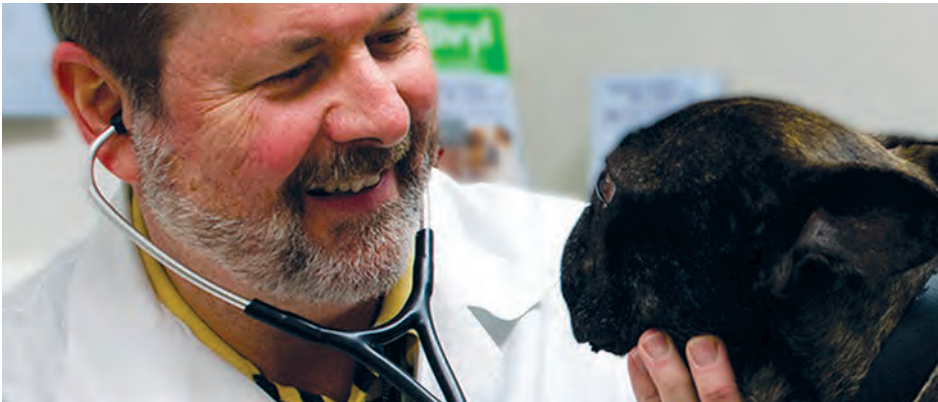
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Why Does Heartworm Incidence Continue to Increase and What Can We Do About It?



Christopher J. Rehm, Sr., DVM, President

The weather is heating up, rains are coming more regularly, termites are swarming, the fleas are exploding, mosquitoes are hatching out in record numbers, new batches of puppies and kittens are coming into our offices for their first checkups, and we are still treating too many poor dogs for the horrific, devastating, and often deadly disease called heartworm or dirofilariasis. The names change but the stories are often very similar. Oh doc, I was too busy to get Buster in last year. I thought Frontline Plus was a heartworm preventive. I was getting some stuff from the feed store that was so much less expensive. I thought my wife was giving Chloe's preventive. Pepper cannot have heartworms because we use preventives every summer. I thought Chester's medicine was the right size for Butch, too. I hear these and other stories all the time but I have never had anyone tell me that they did not think heartworm was important, real, or a threat to their pet.

So why are there more heartworms around the country every year?

Are we not getting the word out? Is there an explanation for what our incidence survey showed, a 21.7% increase on average for heartworm-positive cases per hospital since our last survey? (For more on the 2016 incidence survey and map, please see pages 1 and 7.)

We have many lively discussions about all of the above at our board meetings. We have some of the brightest researchers, teachers, industry veterinarians, parasitologists, cardiologists, and practitioners that can tell you just about every minute detail about the parasite, its life cycle, variations of normal, responses to different stimuli or medications, and prognosticate its next move or where resistance could occur and even postulate why it will occur. Yet we cannot explain or understand why we do not prevent a very preventable disease that affects millions of pets every year. We can explain weather patterns that result in more mosquitoes and the resulting increase in heartworm

infections. We are learning more about the cases of resistance in the Delta and in other parts of the country and feel confident that resistance is not a factor in the increase of heartworm infections and disease. We are confident that we can prevent, treat, and diagnose heartworm infection extremely well. Yet somehow our incidence continues to climb.

What do we do now??

Even though we received some bad news in our 2016 incidence survey, there were some positives gleaned from it as well. More veterinarians and the public are visiting our website and learning more about this parasite. More practitioners are following our Guidelines for treating this disease that Dr. Clarke Atkins calls "the most important disease in veterinary medicine." The AHS App is being used by practitioners and staff for their heartworm cases, calculations, and discussions with their clients. Some states like my home state of Alabama actually had a decrease in heartworm-positive cases since the 2013 survey. I am confident as we come off another April Heartworm Awareness Month and another triennial incidence survey that we can still make a difference for our beloved pets. If anything, I am more determined to fight the good fight and to promote the AHS mission: "To lead the veterinary profession and the public in the understanding of heartworm disease" and our vision of a world without heartworm.

How can you help?

Recruit a colleague to join AHS in our fight against this deadly disease.

Help support research and outreach. Get involved on one of our committees or let us know if you are interested in a board position when one opens up. (For more on AHS activities, please see our Quarterly Report on page 16.)

A wise old veterinarian once said to me, "our clients can afford anything, Chris. They just can't afford everything." That statement had a profound effect on my approach to client education. It is up to us to teach our clients, staff, young associates, and the public how to prioritize for their pets. It is up to us to help them make good choices. It is up to us to make firm, simple recommendations, especially when it comes to parasite prevention. It is also up to us to be sure everyone on our staff sings the same tune so our clients hear the same song and verse at every touch throughout our hospitals, from lodging animal care specialists, to pet nurses, to reception and release.

I love being a veterinarian. After 35 years, I still love getting up in the morning and going to work. Another wise man, my dad, told me not to look at problems as obstacles but as opportunities. We have a huge opportunity to help our clients and our patients every day. Go take advantage of this heartworm opportunity. I know you can do it! ■

– Christopher J. Rehm, Sr., DVM

AHS WELCOMES DR. MARISA AMES TO THE EXECUTIVE BOARD

PLEASE JOIN US in welcoming Dr. Marisa Ames to the AHS Executive Board. Dr. Ames has been an Assistant Professor in the Department of Clinical Sciences at Colorado State University's College of Veterinary Medicine since 2013. A 2007 graduate of the Ohio State University, she completed internships in Small Animal Medicine and Surgery at Michigan State University and in Emergency and Critical Care at Tufts Cummings School of Veterinary Medicine. She completed her cardiology residency in 2012 and the Jane Lewis-Seaks postdoctoral fellowship at North Carolina State University in 2013.

Dr. Ames was appointed to the Board as an Ex Officio (non-voting) member at the Board meeting in March 2017. Rather than going through the typical AHS election process held every three years at the Triennial Symposium, Dr. Ames was named by the Board to fulfill the need for a cardiologist after Dr. Clarke Atkins and Dr. Matt Miller completed their terms of service.

Dr. Ames will serve on the Triennial Symposium Committee along with Dr. Doug Carithers.



Marisa Ames, DVM, Diplomate ACVIM (Cardiology)

COMING SOON!



Parasites & Vectors

THE PROCEEDINGS OF THE 15th TRIENNIAL SYMPOSIUM

will be published this summer as a special issue of the open-source journal *Parasites & Vectors*. This means that for the first time, the proceedings will be available to everyone—not just AHS members—for free!

Watch your inbox for notification of the publication date!



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Indications
SENTINEL[®] SPECTRUM[®] (milbemycin oxime/lufenuron/praziquantel) is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*; for the prevention and control of flea populations (*Ctenocephalides felis*); and for the treatment and control of adult roundworm (*Toxocara canis*, *Toxascaris leonina*), adult hookworm (*Ancylostoma caninum*), adult whipworm (*Trichuris vulpis*), and adult tapeworm (*Taenia pisiformis*, *Echinococcus multilocularis* and *Echinococcus granulosus*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

Dosage and Administration
SENTINEL SPECTRUM should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, 4.55 mg/lb (10 mg/kg) lufenuron, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes.

Dosage Schedule

Body Weight	Milbemycin Oxime per chewable	Lufenuron per chewable	Praziquantel per chewable	Number of chewables
2 to 8 lbs.	2.3 mg	46 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	115 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	230 mg	114 mg	One
50.1 to 100 lbs.	23.0 mg	460 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables			

To ensure adequate absorption, always administer SENTINEL SPECTRUM to dogs immediately after or in conjunction with a normal meal.

SENTINEL SPECTRUM may be offered to the dog by hand or added to a small amount of dog food. The chewables 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 a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

Contraindications
There are no known contraindications to the use of SENTINEL SPECTRUM.

Warnings
Not for use in humans. Keep this and all drugs out of the reach of children.

Precautions
Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention.

Prior to administration of SENTINEL SPECTRUM, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. SENTINEL SPECTRUM is not effective against adult *D. immitis*.

Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Do not use in puppies less than six weeks of age.

Do not use in dogs or puppies less than two pounds of body weight.

The safety of SENTINEL SPECTRUM has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime and lufenuron alone.

Adverse Reactions
The following adverse reactions have been reported in dogs after administration of milbemycin oxime, lufenuron, or praziquantel: vomiting, depression/lethargy, pruritus, urticaria, diarrhea, anorexia, skin congestion, ataxia, convulsions, salivation, and weakness.

To report suspected adverse drug events, contact Virbac at 1-800-338-3659 or the FDA at 1-888-FDA-VETS.

Information for Owner or Person Treating Animal
Echinococcus multilocularis and *Echinococcus granulosus* are tapeworms found in wild canids and domestic dogs. *E. multilocularis* and *E. granulosus* can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where *E. multilocularis* or *E. granulosus* are endemic should be instructed on how to minimize their risk of exposure to these parasites, as well as their dog's risk of exposure. Although SENTINEL SPECTRUM was 100% effective in laboratory studies in dogs against *E. multilocularis* and *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

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02/15

Heartworm Incidence Continued from Page 1

refers to the number of cases of a disease that are present in a particular population at a given time.)

■ **AVERAGE**

The number of cases are averaged for the veterinary clinics and shelters in a geographic area. The averaging is done as multiple entities often serve the same population area, and, in general, each serves somewhat similar numbers. So, averaging helps ensure as much of the population is considered as possible.

■ **REPORTING CLINIC**

The numbers are based on reporting clinics and shelters. If veterinary clinics or shelters do not respond to the survey, we have no idea of your incidence. Without your data, you might consider your local

numbers low, or high, but always bear in mind, the numbers are what were reported.

The most critical important point is to not get caught up in the minutia. Wherever a positive dog is diagnosed, there is a potential that other dogs are at risk. Some areas are higher risk due to weather conditions that lead to high mosquito populations, others are high risk due to high dog concentrations, and other areas have both. Other areas are low risk if these same factors are nonexistent.

When we look across the United States, basically you'll see that wherever people (and pets) are concentrated, heartworms can exist! That is what these maps truly illustrate. ■



WHAT DOES THE
2016 Heartworm Incidence Survey
TELL US?

- The average number of heartworm-positive dogs per practice rose by 21.7%. While this change did not significantly affect the appearance of the incidence map (the map colors reflect ranges), it is a significant finding.
- Go to heartwormsociety.org to compare the new map with maps from 2001, 2004, 2007, 2010, and 2013.
- The top five states in heartworm incidence are Mississippi, Louisiana, Arkansas, Texas, and Tennessee. Rounding out the top ten were South Carolina, Georgia, North Carolina, Alabama, and Florida.
- 23.4% of respondents said heartworm incidence has been up in their practice area since the last survey was conducted three years ago. Reasons cited included poor compliance (failure to give preventives year-round or skipping doses), weather trends that caused an increase in mosquitoes, influx of heartworm-positive dogs from out-of-state, and fewer pet owners giving preventives.
- 19.8% of respondents said heartworm incidence has been down in their practice area since the last survey was conducted three years ago. These practitioners cited improved compliance, more owners giving preventives, and the availability of effective preventive medications. Few respondents cited weather as a factor.
- 77% of respondents follow the AHS guidelines on prevention, diagnosis and treatment of heartworm disease. This is up from 72.5% 3 years ago. Meanwhile, half of all respondents use the AHS website.

ABSTRACTS FROM THE LITERATURE

Examining the role of macrolides and host immunity in combatting filarial parasites

D.S. Carithers

Boehringer Ingelheim, 3239 Satellite Boulevard, Duluth, GA, 30096, USA

From *Parasites & Vectors*. 2017; April 14;10(1):182. doi: 10.1186/s13071-017-2116-6.

Macrocyclic lactones (MLs), specifically the avermectins and milbemycins, are known for their effectiveness against a broad spectrum of disease-causing nematodes and arthropods in humans and animals. In most nematodes, drugs in this class induce paralysis, resulting in starvation, impaired ability to remain associated with their anatomical environment, and death of all life stages. Initially, this was also thought to be the ML mode of action against filarial nematodes, but researchers have not been able to validate these characteristic effects of immobilization/starvation of MLs *in vitro*, even at higher doses than are possible *in vivo*. Relatively recently, ML receptor sites exclusively located proximate to the excretory–secretory (ES) apparatus were identified in *Brugia malayi* microfilaria and an ML-induced suppression of secretory protein release by *B. malayi* microfilariae was demonstrated *in vitro*. It is hypothesized here that suppression of these ES proteins prevents the filarial worm from interfering with the host's complement cascade, reducing the ability of the parasite to evade the immune system. Live microfilariae and/or larvae, thus exposed, are attacked and presented to the host's innate immune mechanisms and are ultimately killed by the immune response, not the ML drug. These live, exposed filarial worms stimulate development of innate, cellular and humoral immune responses that when properly stimulated, are capable of clearing all larvae or microfilariae present in the host, regardless of their individual sensitivity to MLs. Additional research in this area can be expected to improve our understanding of the relationships among filarial worms, MLs, and the host immune system, which likely would have implications in filarial disease management in humans and animals.

KEYWORDS: Avermectin; *Brugia malayi*; *Brugia timori*; *Dirofilaria immitis*; ES proteins; Excretory–secretory apparatus; Filarial worms; Immunity; Ivermectin; Macrocyclic lactones; Macrolides; Milbemycin; *Onchocerca cervicalis*; *Onchocerca volvulus*; *Wuchereria Bancrofti*

Seroprevalence of heartworm infection, risk factors for seropositivity, and frequency of prescribing heartworm preventives for cats in the United States and Canada

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From the *Journal of the American Veterinary Medical Association*. 2017; April 15;250(8):873-880. doi: 10.2460/javma.250.8.873.

OBJECTIVE: To determine the seroprevalence of heartworm infection, risk factors for seropositivity, and frequency of prescribing heartworm preventives for cats.

DESIGN: Prospective cross-sectional study.

ANIMALS: 34,975 cats from 1,353 veterinary clinics (n = 26,707) and 125 animal shelters (8,268) in the United States and Canada.

PROCEDURES: Blood samples were collected from all cats and tested with a point-of-care ELISA for *Dirofilaria immitis* antigen, FeLV antigen, and FIV antibody. Results were compared among geographic regions and various cat groupings.



RESULTS: Seropositivity for heartworm antigen in cats was identified in 35 states but not in Canada; overall seroprevalence in the United States was 0.4%. Seroprevalence of heartworm infection was highest in the southern United States. A 3-fold increase in the proportion of seropositive cats was identified for those with (vs without) outdoor access, and a 2.5-fold increase was identified for cats that were unhealthy (vs healthy) when tested. Seroprevalence was 0.3% in healthy cats, 0.7% in cats with oral disease, 0.9% in cats with abscesses or bite wounds, and 1.0% in cats with respiratory disease. Coinfection with a retrovirus increased the risk of heartworm infection. Heartworm preventives were prescribed for only 12.6% of cats at testing, and prescribing was more common in regions with a higher seroprevalence.

CONCLUSIONS AND CLINICAL RELEVANCE: At an estimated prevalence of 0.4%, hundreds of thousands of cats in the United States are likely infected with heartworms. Given the difficulty in diagnosing infection at all clinically relevant parasite stages and lack of curative treatment options, efforts should be increased to ensure all cats receive heartworm preventives.

Pulmonary hypertension in dogs with heartworm before and after the adulticide protocol recommended by the American Heartworm Society

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From *Veterinary Parasitology*. 2017; March 15;236:34-37. doi: 10.1016/j.vetpar.2017.02.001. Epub 2017 Feb 2.

Pulmonary hypertension (pH) is a frequent and severe phenomenon in heartworm disease (*Dirofilaria immitis*). There is a lack of studies assessing the evolution of the proliferative endarteritis and pH caused by *D. immitis* after the death of the parasites, so this study evaluated the influence that the elimination of the worms exerts over the pulmonary pressure and therefore evolution of the endarteritis, through the evaluation of the Right Pulmonary Artery Distensibility (RPAD) Index and other echocardiographic measurements in 2D mode, M-mode and Doppler echocardiography in 34 dogs naturally infected by *D. immitis* on day 0, and one month after the last adulticide dose (day 120). pH, based on the determination of the RPAD Index, was present in 68% of the dogs (n=23) on day 0 and on day 120. No significant differences were observed between the RPAD Index between the two measurements, and only significant differences were found in pulmonary deceleration time, ejection time, and left ventricular internal diameter in telediastole when measurements from day 0 and day 120 were compared. There was not any worsening in the development of pH after the elimination of the parasites, independently of the parasite burden. During the adulticide treatment, the death of the worms causes thromboembolism and tends to worsen the vascular damage and presence of pH. It seems that following the adulticide protocol recommended by the American Heartworm Society with the previous elimination of *Wolbachia* and reduction of microfilariae followed by the stepped death of the worms did not cause a significant aggravation of the pulmonary damage of the treated dogs. Neither is present any significant improvement in the RPAD Index on day 120; probably, more time is needed before appreciating some positive changes after the elimination of the worms and *Wolbachia* from the vasculature and further studies are necessary.

KEYWORDS: *Dirofilaria immitis*; Echocardiography; Endarteritis; Heartworm; Pulmonary artery; Pulmonary hypertension

Dirofilaria immitis and *D. repens* show circadian co-periodicity in naturally co-infected dogs

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From *Parasites & Vectors*. 2017; February 28;10(1):116. doi: 10.1186/s13071-017-2055-2.

BACKGROUND: *Dirofilaria immitis* and *Dirofilaria repens* are mosquito-borne zoonotic filarioids typically infecting dogs, causing a potentially fatal cardiopulmonary disease and dermatological conditions, respectively. The females are larviparous, releasing the larvae (microfilariae) into the bloodstream, which further develop in mosquito vectors. However, microfilaremia greatly fluctuates during a 24-h period. As the sampling time can greatly influence the accuracy of diagnosis, the aim of the present study was to assess the circadian periodicity of *D. immitis* and *D. repens* in naturally co-infected dogs in an endemic area of Romania and to investigate possible differences of periodicity between these two species.

METHODS: Overall, four dogs harbouring natural co-infection with *D. immitis* and *D. repens* were selected and sampled every two hours for two consecutive days: two dogs in July 2014 and two in July 2015. At each sampling time, a 0.7 ml blood sample was taken. Modified Knott's test was performed on 0.5 ml, and the remaining 0.2 ml were used for DNA extraction and molecular amplification, both in single and duplex PCR reactions. Microfilariae of both species were morphologically identified and counted in each collected sample, microfilaremia was calculated, and fluctuation was charted.

RESULTS: The dynamics of microfilaremia showed similar patterns for both *Dirofilaria* species. In all four dogs, *D. immitis* was present at all sampling times, with several peak values of microfilaremia, of which one was common for all dogs (1 AM), while minimum counts occurred between 5 and 9 AM. Similarly, for *D. repens*, one of the peak values was recorded in all dogs at 1 AM, while minimum counts (including zero) occurred at 9 and 11 AM. Single species-specific PCR reactions were positive for both *D. immitis* and *D. repens* in all collected samples, while duplex PCR failed to amplify *D. repens* DNA in many cases.

CONCLUSIONS: Both *Dirofilaria immitis* and *D. repens* microfilariae are subperiodic, following a similar variation pattern, with peak values of microfilaremia registered during the night in Romania. Duplex PCR fails to identify the infection with *D. repens* in co-infected dogs when the ratio of microfilaremia is in favour of *D. immitis*.

KEYWORDS: Co-infection; *Dirofilaria immitis*; *Dirofilaria repens*; Microfilariae; Periodicity ■





There's new news in the fight against heartworms.

INTRODUCING A NEW HEARTWORM PROTOCOL



There's a new approach in the fight against heartworms. A recent, groundbreaking study conducted by a third-party investigator shows that by repelling and killing mosquitoes, Vectra® 3D was over 99% effective in blocking the transmission of microfilariae from dogs to mosquitoes¹. So why not recommend the flea and tick control that doubles as an extra layer of defense against mosquitoes. It's time to focus on the mosquito – the vector for heartworm.

MAKE DOUBLE DEFENSE — VECTRA® 3D PLUS A HEARTWORM PREVENTIVE — YOUR NEW PROTOCOL.

DO NOT USE VECTRA® 3D ON CATS.

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Double Defense logo™ trademark is the property of Ceva Animal Health, LLC

¹J.W. McCall, E. Hodgkins, M. Varlout, A. Mansour, U. DiCosty. Inhibition of the transmission of *Dirofilaria immitis* to mosquitoes by weekly exposure of microfilaremic dogs treated topically with dinotefuran-pyrimethrin-pyriproxyfen to uninfected *Aedes aegypti*.

To see the new study go to FightHeartwormNow.com.

3 in 1

parasite protection

FLEAS • HEARTWORMS
INTESTINAL PARASITES



Proven protection inside and out



Triflexis is the
#1 prescribed
canine
combination
parasiticide¹

More than **90 million doses** dispensed²

Triflexis 
(spinosad + milbemycin oxime)



Indications

Triflexis is indicated for the prevention of heartworm disease (*Dirofilaria immitis*). Triflexis kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), and the treatment and control of adult hookworm (*Ancylostoma caninum*), adult roundworm (*Toxocara canis* and *Toxascaris leonina*) and adult whipworm (*Trichuris vulpis*) infections in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater.

Important Safety Information

Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with spinosad alone, one of the components of Triflexis. Treatment with fewer than three monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention. Prior to administration of Triflexis, dogs should be tested for existing heartworm infection. Use with caution in breeding females. The safe use of Triflexis in breeding males has not been evaluated. Use with caution in dogs with pre-existing epilepsy.

The most common adverse reactions reported are vomiting, lethargy, pruritus, anorexia and diarrhea. To ensure heartworm prevention, dogs should be observed for one hour after administration. If vomiting occurs within one hour, redose. Puppies less than 14 weeks of age may experience a higher rate of vomiting. For product information, including complete safety information, see page XX.

¹Vet Insite Analytics December, 2015. Based on total canine combination parasiticide product data (flea, tick, heartworm). ²Elanco Data on File, July, 2015.

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Elanco

TRIFEXIS®
(spinosad + milbemycin oxime)
Chewable Tablets

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Before using TRIFEXIS chewable tablets, please consult the product insert, a summary of which follows:

Indications:
TRIFEXIS is indicated for the prevention of heartworm disease (*Dirofilaria immitis*), TRIFEXIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), and the treatment and control of adult hookworm (*Ancylostoma caninum*), adult roundworm (*Toxocara canis* and *Toxascaris leonina*) and adult whipworm (*Trichuris vulpis*) infections in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater.

Dosage and Administration:
TRIFEXIS is given orally, once a month at the minimum dosage of 13.5 mg/lb (30 mg/kg) spinosad and 0.2 mg/lb (0.5 mg/kg) milbemycin oxime body weight. For heartworm prevention, give once monthly for at least 3 months after exposure to mosquitoes (see **EFFECTIVENESS**).

Contraindications:
There are no known contraindications to the use of TRIFEXIS.

Warnings:
Not for human use. Keep this and all drugs out of the reach of children. Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS (see **ADVERSE REACTIONS**).

Precautions:
Treatment with fewer than 3 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see **EFFECTIVENESS**).

Prior to administration of TRIFEXIS, 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. TRIFEXIS is not effective against adult *D. immitis*. While the number of circulating microfilariae may decrease following treatment, TRIFEXIS is not indicated for microfilariae clearance.

Mild, transient hypersensitivity reactions manifested as labored respiration, vomiting, salivation and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Use with caution in breeding females. The safe use of TRIFEXIS in breeding males has not been evaluated.

Use with caution in dogs with pre-existing epilepsy (see **ADVERSE REACTIONS**). Puppies less than 14 weeks of age may experience a higher rate of vomiting.

Adverse Reactions:
In a well-controlled US field study, which included a total of 352 dogs (176 treated with TRIFEXIS and 176 treated with an active control), no serious adverse reactions were attributed to administration of TRIFEXIS. All reactions were regarded as mild.

Over the 180-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence >1% (average monthly rate) within any of the 6 months of observation are presented in the following table. The most frequently reported adverse reaction in dogs in the TRIFEXIS group was vomiting.

Average Monthly Rate (%) of Dogs With Adverse Reactions

Adverse Reaction	TRIFEXIS Chewable Tablets ^a	Active Control Tablets ^a
Vomiting	6.13	3.08
Pruritus	4.00	4.91
Lethargy	2.63	1.54
Diarrhea	2.25	1.54
Dermatitis	1.47	1.45
Skin Reddening	1.37	1.28
Decreased appetite	1.27	1.35
Pinna Reddening	1.18	0.87

^an=176 dogs

In the US field study, one dog administered TRIFEXIS experienced a single mild seizure 2 ½ hours after receiving the second monthly dose. The dog remained enrolled and received four additional monthly doses after the event and completed the study without further incident.

Following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS, some dogs have experienced the following clinical signs: trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation. Spinosad alone has been shown to be safe when administered concurrently with heartworm preventives at label directions. In US and European field studies, no dogs experienced seizures when dosed with spinosad alone at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of spinosad, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

For technical assistance or to report suspected adverse drug events, contact Elanco Animal Health at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VECS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>

Post Approval Experience (Mar 2012):
The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, pruritus, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening.

Effectiveness:

Heartworm Prevention:
In a well-controlled laboratory study, TRIFEXIS was 100% effective against induced heartworm infections when administered for 3 consecutive monthly doses. Two consecutive monthly doses did not provide 100% effectiveness against heartworm infection. In another well-controlled laboratory study, a single dose of TRIFEXIS was 100% effective against induced heartworm infections.

In a well-controlled six-month US field study conducted with TRIFEXIS, no dogs were positive for heartworm infection as determined by heartworm antigen testing performed at the end of the study and again three months later.

Flea Treatment and Prevention:
In a well-controlled laboratory study, TRIFEXIS demonstrated 100% effectiveness on the first day following treatment and 100% effectiveness on Day 30.

In a well-controlled laboratory study, spinosad, a component of TRIFEXIS, began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. Spinosad, a component of TRIFEXIS, kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with spinosad alone. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis and pruritus as a direct result of eliminating the fleas.

Treatment and Control of Intestinal Nematode Infections:
In well-controlled laboratory studies, TRIFEXIS was ≥ 80% effective in removing naturally and experimentally induced adult roundworm, whipworm and hookworm infections.

Palatability:

TRIFEXIS is a flavored chewable tablet. In a field study of client-owned dogs where 175 dogs were each offered TRIFEXIS once a month for 6 months, dogs voluntarily consumed 54% of the doses when offered plain as if a treat, and 33% of the doses when offered in or on food. The remaining 13% of doses were administered like other tablet medications.

NADA 141-321, Approved by the FDA
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Indianapolis, IN 46285
www.trifexis.com

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Sep 2014 038049_Mkt4

HEARTWORM UNIVERSITY UPDATE

HEARTWORM UNIVERSITY RETURNS IN AUGUST



HEARTWORM UNIVERSITY

AMERICAN HEARTWORM SOCIETY™

A six-hour session of Heartworm University will take place on August 12, 2017 in Hershey, Pennsylvania in conjunction with the Keystone Veterinary Conference. Hosted by CEVA, the program will be presented by Dr. Matt Miller.

For more information, please go to <http://keystonevetconference.org>.



LOOKING AHEAD...

Two additional sessions of Heartworm University are now scheduled for 2018. On February 25, 2018, HWU will be presented in Nashville, Tennessee in conjunction with the Music City Veterinary Conference. On March 18, 2018, Heartworm University is scheduled at the Louisiana State VMA in Baton Rouge, Louisiana. Both sessions will be presented by Dr. Clarke Atkins. ■

Did you know...

AHS OFFERS FREE STUDENT MEMBERSHIPS FOR ALL ACTIVE UNDERGRADUATE AND POST-GRADUATE VETERINARY STUDENTS

The American Heartworm Society is dedicated to serving all veterinary professionals—including students. Currently AHS has 357 student members. Student members are solicited through list serves (including AAVP) and through direct mail to each veterinary school.

Benefits offered to student members include

- Quarterly AHS Bulletin delivered to their university email address
- Access to all paid-member online resources at heartwormsociety.org
- Reduced pricing on certain educational materials available through our online store

Students can register for membership by going to <https://heartwormsociety.org/student-subscription>. After the registration form is completed, AHS will verify the applicant's status as a student before approving the account. Student memberships are renewable for one year at a time as long as the member is a current veterinary student.

JACK'S LEGACY

Heartbreak of Adopted Dog's Death Inspires Family to Educate Pet Adopters on Heartworm Prevention



The American Heartworm Society recently received a generous donation check from a fundraiser held in memory of Jack, a dog adopted in December 2016 from the Humane Society of Greenwood, South Carolina by Candace and Richard Borland. Candace's daughter, Shannon Cohen, works as an adoption counselor at the shelter; she knew her parents had been looking for a dog for a long time and felt Jack was perfect for them. The Borlands knew that Jack tested positive for heartworms but believed that once his treatment was completed he would be fine. Sadly, Jack did not survive the treatment due to the severity of the disease and died less than 3 months later. The family was heartbroken.

Jack's death inspired Shannon to learn more about heartworm disease and prevention and she now shares her knowledge with potential adopters who come in to the Humane Society shelter. For her birthday, Shannon set up an online fundraiser and asked friends and family, instead of giving presents or sending cards, to make a donation to the American Heartworm Society. When the check arrived, we were eager to learn more about Jack's story. The narrative that Shannon posted on Facebook for the fundraiser appears on the following page

During his short time with the Borlands, Jack clearly left his mark on many people who loved him dearly. The decision to adopt a heartworm-positive dog and go through all that heartworm treatment entails is not an easy one. Candace and Richard Borland and Shannon Cohen truly are Heartworm Heroes. The American Heartworm Society thanks you for your generous donation and is honored to support you in achieving Jack's legacy—eliminating unnecessary suffering in other dogs by educating pet owners and adopters about this entirely preventable disease.

Note: This fundraiser has ended. Those who wish to make donations or hold their own fundraiser in memory of a beloved pet can contact AHS at info@heartwormsociety.org.

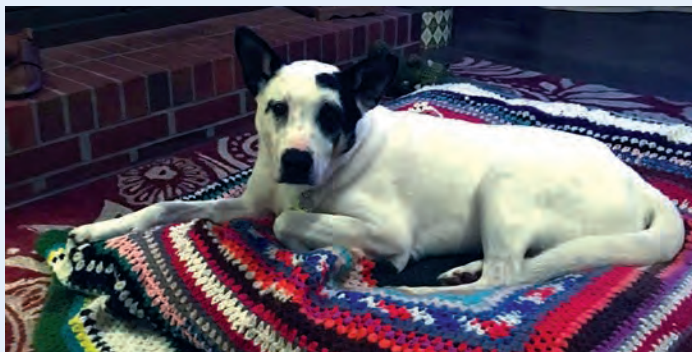
JACK'S STORY

As posted on Facebook
by Shannon Cohen

"Today we lost a very special member of our family. Jack, a 5-year-old shepherd mix, was adopted by my mom and step dad at Christmas from the Humane Society of Greenwood. Jack was special for many reasons, but a unique adoption because of his diagnosis with heartworms. They adopted him as a special needs dog knowing he would need the treatment. They not only wanted to cure him of the disease, but wanted to give him a chance to feel loved and have a family for the first time in his life. You see, before coming to the Humane Society, Jack spent his life on a chain. His bottom teeth were filed down from eating rocks and chewing on the chain, and the tips of his ears were hairless from flies biting them over and over again. Jack was so lucky to be given a second chance, unlike so many other dogs.



Unfortunately, along with the physical neglect he suffered, he also was neglected medically and did not receive heartworm preventive. And as such, needed to receive the very painful "fast kill" treatment in order to survive. After 4 weeks at his new home and blossoming into pretty much the happiest dog I've ever seen, he was taken in to receive the treatment on February 2nd and 3rd, 2017. He was not the same dog after this.



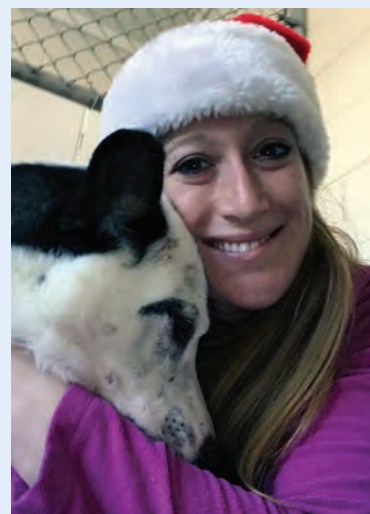
Jack experienced declining health since receiving the treatment. His endless tail wags and smiles turned into complete lifelessness and suffering, not only for him, but for my family who had to watch. Jack experienced fluid buildup in his lungs and stomach, and was not able to eat or drink despite the multiple vet visits, medicine, and

force feeding that my parents had to do. He continued to decline for 2.5 weeks as we all watched, and prayed, and tried to remain hopeful. Finally, he was admitted into the hospital on February 20th and spent 24 hours with constant monitoring and an IV. Despite these measures, Jack continued to decline only to be determined that he must have been in such late stages of the disease that only heart surgery could have saved him. As his organs would start shutting down soon, they had to make the decision to end his suffering.

The purpose of this fundraiser is to support the research and education being done by the American Heartworm Society, and prevent the suffering of helpless animals like Jack. I hope that the heartbreak from this experience can be used in a positive way by helping to educate pet owners on the disease and that dogs should be on a regular monthly preventative.

I have always kept my dogs on heartworm preventative, but have known very little about the disease until this experience. Heartworms are spread from animal to animal by mosquitoes after biting infected hosts and then carrying the blood to an unaffected animal and biting them. Because it is carried by mosquitoes, the disease is much more prevalent in warmer, moist climates such as the southeastern US. For more information on heartworm disease, please visit the American Heartworm Society website at www.heartwormsociety.org.

My birthday is on February 26, and I ask that instead of presents or cards or even time you may spend sending me a text or FB message, please just donate whatever you can, even if only \$1.00, to this fundraiser." ■



WHAT'S NEW FROM AHS THIS SUMMER?

A QUARTERLY UPDATE ON AHS PROGRAMS AND RESOURCES

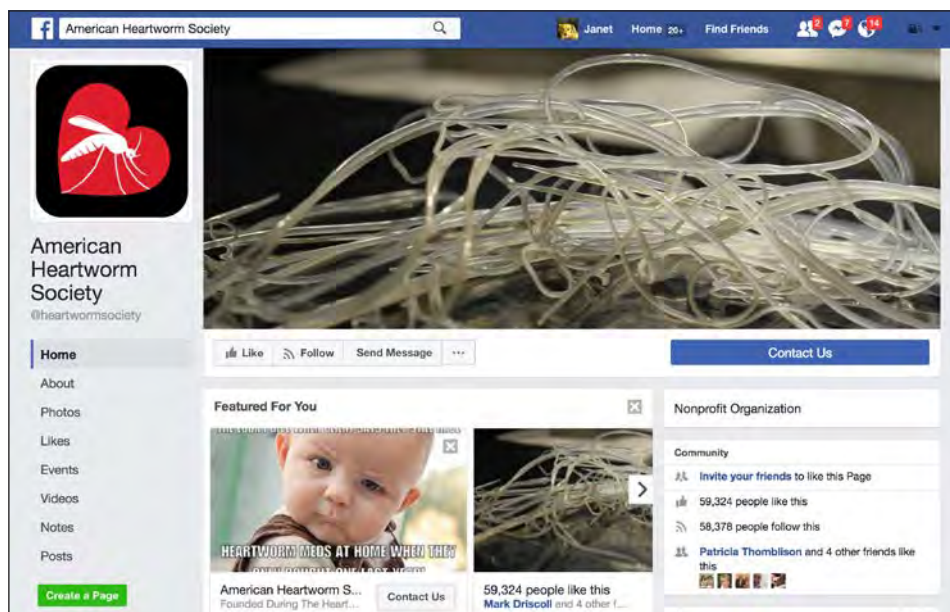


Much of our activity this spring has been centered around the release of the 2016 Heartworm Incidence Survey results and map in April during Heartworm Awareness Month. For more on the survey results and interpretation of the map, see Infographics and Red Hots below and pages 1 and 7 of this issue of the Bulletin.

HEARTWORM AWARENESS MONTH

April is prime time for outreach on heartworm disease and we stepped up our efforts with media outreach, social media engagement and direct outreach to veterinarians.

- **Media outreach** focused on the 2016 incidence survey and the 2016 heartworm incidence map. We created a veterinary news release as well as a consumer version in order to reach both professional and pet-owner audiences. Veterinary clinics also picked up on the story, customizing the news for their own audiences.
- **Social media outreach** included daily posting and tweeting on our Facebook and Twitter pages. We also ran a month-long Facebook campaign to boost the size of that community. As of mid-May, we have 59,320 “likes” (a gain over more than 6,000 likes since April 1) on Facebook and 5,590 followers on Twitter—a gain of several hundred followers in the same time frame. One of our most popular posts was the announce-



ment of the new AHS incidence map, which reached almost 190,000 people on Facebook alone, and garnered more than 1,700 shares, 252 comments and almost 1,500 “likes.” The map also garnered a number of retweets and “favorites” on Twitter.

INFOGRAPHICS

A new infographic (see facing page 17 or go to heartwormsociety.org) that details AHS incidence survey findings beyond the incidence map, including a

second map showing incidence trends and insights behind those trends can be downloaded at heartwormsociety.org. Be sure to check it out, download it, and share it.

RED HOTS

Red Hots are e-blasts sent out to inform veterinarians of important news or developments related to heartworm. Two were sent out this spring, one in late March on heartworm treatment and one in April on the Incidence map.

■ Clarification of Heartworm Treatment Guidelines: Melarsomine is the Adulticide Drug of Choice

In response to numerous inquiries from veterinarians on alternatives to adulticide treatment, we sent out a Red Hot e-blast stressing the importance of melarsomine in the AHS protocol for treatment of adult infections. With two melarsomine products now on the market, it is now easier than ever to follow the treatment guidelines,

Continues on Page 22

HEARTWORM IN SHELTER ANIMALS

AHS PARTNERS WITH THE ASSOCIATION OF SHELTER VETERINARIANS TO PRODUCE TWO NEW PET ADOPTION BROCHURES

The Heartworm Disease Resource Task Force, a partnership between The Association of Shelter Veterinarians (ASV) and American Heartworm Society (AHS), has released two additional client educational brochures on heartworm for people seeking to adopt a shelter animal. The first three brochures in the series covered three adoption scenarios:

- **What You Need to Know About Heartworms and Your Newly Adopted Dog** (for shelters that are unable to test for or treat canine heartworm disease)
- **Are You Adopting a Heartworm-Positive Dog?** (for shelters that are unable to treat canine heartworm disease)
- **What You Need to Know About Heartworm Treatment and Your Newly Adopted Dog** (for shelters that treat canine heartworm disease)

The two new brochures focus on:

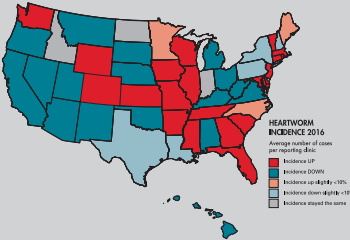
- **What Does a “Negative” Heartworm Test Mean?**
- **Are You Adopting a Dog from Another Area of the Country?** (for shelters that relocate dogs from heartworm-endemic regions)

The sixth and final brochure in this series, on feline heartworm disease, will be available soon.

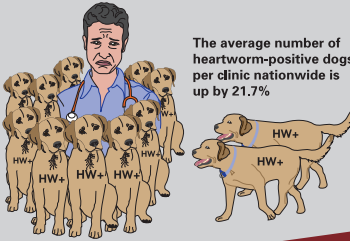
These illustrated, professionally designed brochures are available for download from <https://heartwormsociety.org/veterinary-resources/shelter-resources>.

Is Heartworm Incidence ↑ or ↓?

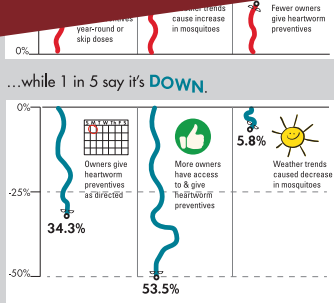
TRENDING TOPIC. Veterinarians in all 50 states were asked whether heartworm incidence is **UP** or **DOWN** in the past 3 years.



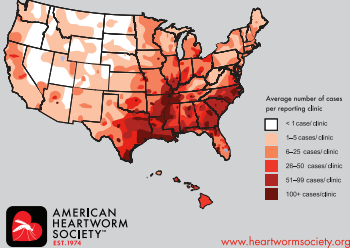
TEST RESULTS IN. Since 2013, the average number of dogs per veterinary clinic testing heartworm-positive has risen.



NEW INFOGRAPHIC AVAILABLE NOW AS FREE DOWNLOAD!



WHERE THE HEARTWORMS ARE. Thousands of veterinary practices submitted data to make this map. Check out the incidence in your area.



PROTECT YOUR PET FROM HEARTWORM 12 MONTHS A YEAR. TEST FOR HEARTWORM EVERY 12 MONTHS.

What Does a “Negative” Heartworm Test Mean?

Keep Them Safe. Love Them Always.

Prepared by the American Heartworm Society and the Association of Shelter Veterinarians

Are You Adopting a Dog from Another Area of the Country?

Keep Them Safe. Love Them Always.

Prepared by the American Heartworm Society and the Association of Shelter Veterinarians

AVAILABLE NOW AS FREE DOWNLOADS!

TRUST.

¹ Data on file at Merial.
² Freedom of Information: NADA140-971 (January 15, 1993).



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- ✓ PREVENTS HEARTWORM DISEASE
- ✓ TREATS AND CONTROLS 3 SPECIES OF HOOKWORMS
- ✓ TREATS AND CONTROLS 2 SPECIES OF ROUNDWORMS
- ✓ OWNERS PREFER IT¹ AND DOGS LOVE IT²



IMPORTANT SAFETY INFORMATION: HEARTGARD® Plus (ivermectin/pyrantel) is well tolerated. All dogs should be tested for heartworm infection before starting a preventive program. Following the use of HEARTGARD Plus, digestive and neurological side effects have rarely been reported. For more information, please visit www.HEARTGARD.com.

Heartgard®
(ivermectin/pyrantel) **Plus**

HEARTWORM EDUCATION

NCSU VETERINARY STUDENTS EDUCATE THE PUBLIC ABOUT HEARTWORM DISEASE AT ANNUAL OPEN HOUSE

Thousands of visitors of all ages toured the Veterinary Hospital, classrooms, and laboratories at NC State University's College of Veterinary Medicine during their annual Open House held on April 1, 2017. The day included interesting demonstrations; fun and informative presentations on pet health; an opportunity to talk with faculty, staff, and students; and a chance to get up close with animals large and small.

AHS Board Member Dr. Jenni Rizzo provided AHS resources for the Parasitology Lab's display on heartworm disease (see photo) to Caroline Brewer, Class of 2019 and AHS Student Liaison at North Carolina State University College of Veterinary Medicine. In addition to the AHS canine and feline brochures, life cycle diagrams, and posters, Caroline reports that "We also had a coloring area for kids where we had a couple of the coloring pages you provided links for. Thank you for your help and donations!"



Heartgard[®] Plus
(ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal (U.S.A.) 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 ascarids (*Toxocara canis*, *Toxascaris leonina*) and hookworms (*Ancylostoma caninum*, *Uncinaria stenocephala*, *Ancylostoma braziliense*).

DOSAGE: HEARTGARD[®] Plus (ivermectin/pyrantel) 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 ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older. For dogs over 100 lb use the appropriate combination of these 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 HEARTGARD Plus 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.

HEARTGARD Plus 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 HEARTGARD Plus 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 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 HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*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: HEARTGARD Plus 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. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis*, *T. leonina*) and hookworms (*A. caninum*, *U. stenocephala*, *A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus 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.

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 between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, 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 HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). 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) 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. HEARTGARD 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 HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus 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 HEARTGARD Plus in a heartworm disease prevention 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: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

For customer service, please contact Merial at 1-888-637-4251.



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Brief Summary of Prescribing Information

DIROBAN™
Canine Heartworm Treatment

Sterile Powder for Injection

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

WARNING
DIROBAN should be administered by deep intramuscular injection ONLY in the epaxial (lumbar) muscles (L₂ - L₃).
DO NOT USE IN ANY OTHER MUSCLE GROUP. DO NOT USE INTRAVENOUSLY.
Care should be taken to avoid superficial injection or leakage (see SAFETY).

INDICATIONS

DIROBAN Sterile Powder for Injection is indicated for the treatment of stabilized Class 1^a, 2^b, and 3^c heartworm disease caused by immature (4 month-old, stage L₃) to mature adult infections of *Dirofilaria immitis* in dogs.

Heartworm Disease Classification: The following parameters were used to classify the dogs in the clinical field trials for DIROBAN. Other parameters may be considered. As a general rule, conservative treatment should be employed since heartworm disease is serious and potentially fatal. If there is evidence of a high worm burden, patients should be categorized as Class 3.

^a Class 1: Patients in this category are characterized as having asymptomatic to mild heartworm disease. No radiographic signs or signs of anemia are evident. Mild proteinuria (2+) may be present. Radiographic signs may include a general loss of condition, fatigue on exercise, or occasional cough; however, no objective radiographic or other abnormal laboratory parameters will be present.

^b Class 2: Patients in this category are characterized as having moderate heartworm disease. Radiographic signs or signs of anemia [Packed Cell Volume (PCV) less than 30% but greater than 20%, or other hematologic parameters below normal] are evident. Mild proteinuria (2+) may be present. Radiographic signs may include right ventricular enlargement, slight pulmonary artery enlargement, or circumscribed perivascular densities plus mixed alveolar/interstitial lesions. Patients may be free of subjective clinical signs or may have a general loss of condition, fatigue on exercise, or occasional cough. If necessary, patients should be stabilized prior to treatment.

^c Class 3: Patients in this category are characterized as having severe heartworm disease. These patients have a guarded prognosis. Subjective signs of disease may include cardiac cachexia (wasting), constant fatigue, persistent cough, dyspnea, or other signs associated with right heart failure such as ascites and/or jugular pulse. Radiographic signs may include right ventricular enlargement or right ventricular plus right atrial enlargement, severe pulmonary artery enlargement, circumscribed to chronic mixed patterns and diffuse patterns of pulmonary densities or radiographic signs of thromboembolism. Signs of significant anemia (PCV <20% or other hematologic abnormalities) may be present. Proteinuria (> 2+) may be present. Patients may have only moderate clinical signs and significant laboratory or radiographic alterations or they may have significant clinical signs with only moderate laboratory and radiographic signs and be categorized as Class 3. Patients in Class 3 should be stabilized prior to treatment and then administered the alternate dosing regime (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

DIROBAN is contraindicated in dogs with very severe (Class 4) heartworm disease. Patients in this category have Caval Syndrome (*D. immitis* present in the venae cavae and right atrium).

WARNINGS

(See boxed Warning.) For use in dogs only. Safety for use in breeding animals and lactating or pregnant bitches has not been determined.

HUMAN WARNINGS

Keep this and all medications out of the reach of children. Avoid human exposure. Wash hands thoroughly after use or wear gloves. Potentially irritating to eyes. Rinse eyes with copious amounts of water if exposed. Consult a physician in cases of accidental exposure by any route (dermal, oral, or by injection).

The Safety Data Sheet (SDS) contains more detailed occupational safety information. To report adverse effects, obtain a SDS or for assistance, contact Zoetis Inc. at 1-888-963-8471.

PRECAUTIONS

General: All dogs with heartworm disease are at risk for post-treatment pulmonary thromboembolism (death of worms which may result in fever, weakness, and coughing), though dogs with severe pulmonary arterial disease have an increased risk and may exhibit more severe signs (dyspnea, hemoptysis, right heart failure and possibly death). Dogs should be restricted from light to heavy exercise post-treatment depending on the severity of their heartworm disease.

Studies in healthy (heartworm negative) dogs indicate that adverse reactions may occur after the second injection in the series even if no problems were encountered with the first injection. All patients should be closely monitored during treatment and for up to 24 hours after the last injection.

Special Considerations for Class 3 dogs: Following stabilization, severely ill (Class 3) dogs should be treated according to the alternate dosing regime in an attempt to decrease post-treatment mortality associated with thromboembolism (see **DOSAGE AND ADMINISTRATION**). Post-treatment mortality due to thromboembolism and/or progression of the underlying disease may occur in 10 to 20% of the Class 3 patients treated with DIROBAN (see **Mortality**). Hospitalization post-treatment and strict exercise restriction are recommended. Other supportive therapies should be considered on a case-by-case basis. If the alternate dosing regime is used, expect increased injection site reactions on the side receiving the second injection since the skeletal muscles at the first injection site may not have fully recovered (healed). If persistent swelling is present at 1 month, the second injections may be delayed for several weeks up to 1 month.

Special Considerations for Older Dogs: In clinical field trials, dogs 8 years or older experienced more post-treatment depression/lethargy, anorexia/inappetence, and vomiting than younger dogs.

ADVERSE REACTIONS (SIDE EFFECTS)

Injection Sites: At the recommended dosage in clinical field trials, significant irritation was observed at the intramuscular injection sites, accompanied by pain, swelling, tenderness, and reluctance to move. Approximately 30% of treated dogs experienced some kind of reaction at the injection site(s). Though injection site reactions were generally mild to moderate in severity and recovery occurred in 1 week to 1 month, severe reactions did occur (< 1.0%), so care should be taken to avoid superficial or subcutaneous injection and leakage. Firm nodules can persist indefinitely.

Other Reactions: Coughing/gagging, depression/lethargy, anorexia/inappetence, fever, lung congestion, and vomiting were the most common reactions observed in dogs treated with melarsomine dihydrochloride. Hypersalivation and panting occurred rarely in clinical trials (1.9% and 1.6%, respectively); however, these signs may occur within 30 minutes of injection and may be severe. One dog vomited after each injection of melarsomine dihydrochloride, despite pretreatment with anti-emetics. All adverse reactions resolved with time or treatment with the exception of a limited number of injection site reactions (persistent nodules, see Table: **Average Onset Time and Duration (with Ranges) of the Most Common Reactions in Clinical Trials**) and a low number of post-treatment deaths (see **Mortality**).

Prevalence of Clinical Observations/Adverse Reactions Reported in Clinical Field Trials: The following table enumerates adverse events that occurred in 1.5% or more of dogs with Class 1, 2, and 3 heartworm disease treated with melarsomine dihydrochloride in clinical field trials. Comparison is made with the same adverse events reported in dogs treated with placebo. Some of the following clinical observations/adverse reactions seen in dogs treated with melarsomine dihydrochloride may be directly attributable to the drug or they may be secondary to worm death and/or the underlying heartworm disease process.

Prevalence of Clinical Observation/Adverse Reactions Reported in Clinical Field Trials		
Clinical Observation/Adverse Reaction	Melarsomine dihydrochloride % of dogs n=311	PLACEBO % of dogs n=63
Injection Site Reactions	32.8	3.2
Coughing/Gagging	22.2	14.3
Depression/Lethargy	15.4	4.8
Anorexia/Inappetence	13.2	3.2
Pyrexia (fever)	7.4	0.0
Lung Congestion/Sounds	5.5	1.6
Emesis	5.1	1.6
Diarrhea	2.6	0.0
Dyspnea	2.6	1.6
Hypersalivation	1.9	0.0
Panting	1.6	0.0
Hemoptysis	1.6	0.0

Clinical observations/adverse reactions occurring in less than 1.5% of the dogs treated with melarsomine dihydrochloride include: abdominal hemorrhage, abdominal pain, bloody stool/diarrhea, colitis, gingivitis, pancreatitis, anemia, DIC, hemoglobinemia, icterus (mucous membranes), discolored urine, hematuria, inappropriate urination, low specific gravity, polyuria, pyuria, bronchitis, miscellaneous respiratory problem, pneumonia, tachypnea, tracheobronchitis, wheezing, alopecia, hair color and coat character change, miscellaneous skin problem, ataxia, disorientation, fatigue/tires easily, miscellaneous eye problem, weight loss, convulsion/seizure, leukocytosis, polydipsia, and restlessness.

Onset and Duration of Clinical Observations/Adverse Reactions: The following table is provided to show the average onset time post-treatment for the most common reactions and the average duration of each event, as calculated from the 311 dogs treated with melarsomine dihydrochloride in the clinical field trials.

Average Onset Time and Duration (with Ranges) of the Most Common Reactions in Clinical Trials

Clinical Observation/Adverse Reaction	Avg. Onset Time in Days (range)*	Avg. Duration in Days (range)*
Injection Site		
Swelling/Edema/Seroma	6 (0*-77)	18 (<1-210)
Pain/Discomfort/ Irritation/Inflammation/Heat	1 (0-6)	3 (<1-30)
Generalized/Local Myalgia with Tenderness and Stiffness	3 (1-8)	9 (<1-30)
Persistent (lumps, knots, nodules, masses)	22 (0-99)	47 (1-152)
Abscess (sterile and septic)	24 (10-42)	21 (5-36)
Coughing/Gagging	10 (0-103)	13 (<1-134)
Depression/Lethargy	5 (0-46)	6 (<1-48)
Anorexia/Inappetence	5 (0-63)	5 (<1-30)

*A zero indicates that the reaction first occurred on the day of treatment.

Mortality: Death is a possible sequelae of heartworm disease in dogs with or without treatment, especially in the Class 3 dogs. The following table shows the percentage of dogs that died in clinical trials with melarsomine dihydrochloride and the causes of death, if known.

Mortality in Dogs with Class 1, 2, and 3 Heartworm Disease Treated with melarsomine dihydrochloride in Clinical Field Trials		
	CLASS 1, 2 % OF DOGS n=267	CLASS 3 % OF DOGS n=44
Total Deaths	5.2	18.2
Cause:		
Trauma	2.3	2.3
Thromboembolism	0.0	4.6
Euthanasia (unrelated to treatment or underlying disease)	1.1	0.0
Euthanasia (related to treatment or underlying disease)	0.0	2.3
Underlying Disease	0.8	2.3
Undetermined	1.1	6.8

In one small (n=15), uncontrolled field study in severely ill (Class 3) dogs, 5 dogs died following treatment. Pulmonary thromboembolism was the cause of one death. The remaining dogs were not necropsied. All 5 dogs were in right heart failure at the time of treatment. Clinical signs seen in this study which were not seen in the larger studies include atrial fibrillation, collapse, hypothermia, and weakness.

Post Approval Experience: In addition to the aforementioned adverse reactions reported in pre-approval clinical studies, there have also been rare reports of paresis and paralysis in dogs following administration of melarsomine dihydrochloride. To report a suspected adverse reaction, contact Zoetis Inc. at 1-888-963-8471.

Overdosage: Three dogs were inadvertently overdosed with melarsomine dihydrochloride in the clinical field trials when the dose was calculated on a mg/lb basis rather than a mg/kg basis (2X overdosage). Within 30 minutes of injection, one dog showed excessive salivation, panting, restlessness, and fever with all signs resolving within 4 hours. Vomiting and diarrhea were seen in the second dog within 24 hours of injection. The dog vomited once and the diarrhea resolved within 24 hours. The third dog showed no systemic reaction to the overdosage. Clinical observations in healthy beagle dogs after receiving up to 3X the recommended dose included tremors, lethargy, unsteadiness/ataxia, restlessness, panting, shallow and labored respiration, rales, severe salivation, and vomiting which progressed to respiratory distress, collapse, cyanosis, stupor, and death (see **SAFETY**).

BAL in Oil Ampules (Dimercaprol Injection, USP) [Akorn, San Clemente, California, at 1-800-223-9851] is reported in the literature to be an antidote for arsenic toxicity and was shown in one study to reduce the signs of toxicity associated with overdosage of melarsomine dihydrochloride. The efficacy of melarsomine dihydrochloride may be reduced with co-administration of BAL.

STORAGE CONDITIONS

Store upright at room temperature (15° - 30°C). After reconstitution, solutions should be stored under refrigeration and kept from light in the original packaging for 36 hours. Do not freeze reconstituted solution.

HOW SUPPLIED

DIROBAN is provided as 5 - 50 mg vials of lyophilized melarsomine dihydrochloride with accompanying 5 - 2 mL vials of sterile water for injection USP.

ANADA 200-609, Approved by FDA



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Kalamazoo, MI 49007
August 2016

30559700A&P

Reliable heartworm treatment. Now with reliable availability.

NEW from Zoetis—**DIROBAN™** (melarsomine dihydrochloride)

A heartworm positive diagnosis is serious business. Treatment can be scary for the client, traumatic for the pet and stressful for you and your staff. Having dependable access to an FDA-approved adulticide now means one less thing for you to worry about.

Speak with your Zoetis representative to learn more and visit learnaboutDiroban.com for pet owner tools.

**DIROBAN™**
(melarsomine dihydrochloride)



IMPORTANT SAFETY INFORMATION: DIROBAN is for use in dogs only. Do not use in dogs with very severe (Class 4) heartworm disease. Avoid human exposure. Consult a physician in cases of accidental human exposure by any route. **DIROBAN should be administered by deep intramuscular injection in the lumbar (epaxial) muscles (L₃ – L₅) ONLY. DO NOT USE IN ANY OTHER MUSCLE GROUP. DO NOT USE INTRAVENOUSLY.** Care should be taken to avoid superficial injection or leakage. Safety for use in breeding, pregnant or lactating animals has not been determined. Common side effects include injection site irritation (accompanied by pain, swelling, tenderness and reluctance to move), coughing/gagging, depression/lethargy, anorexia/inappetence, fever, lung congestion and vomiting. All patients should be monitored during treatment and for up to 24 hours after the last injection. See Brief Summary of Prescribing Information for additional safety information and precautions on page 27.

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zoetis

- **2016 Heartworm Incidence Survey: The GOOD, the BAD, and the UGLY** A veterinary e-blast was distributed to almost 34,000 companion animal veterinarians featuring the new incidence map and some statistics on findings from the survey (see page 7 for selected survey results).



COLLABORATION WITH THE ASV

- **Adoption Brochures** The Heartworm Disease Resource Task Force, a partnership between AHS and Association of Shelter Veterinarians (ASV), released two additional client educational brochures this spring on heartworm for people seeking to adopt a shelter animal. For more on this series of six brochures, see page 23.

AHS IN THE NEWS

- In 2017, we are continuing our “Heartworm Hotline” series in *Today’s Veterinary Practice*. The May/June article, which was co-authored by AHS Board member Dr. Chris Duke and CVT Kathleen Williston, focused on the team approach needed for heartworm education; the July/August article, which is authored by AHS Board member Dr. Brian DiGangi, will cover the role of heat pretreatment of serum samples in heartworm diagnosis, and the September/October issue will feature an expanded summary of the AHS incidence survey results.
- The “AHS Quarterly” series continues in *Clinician’s Brief*. The April issue provided an overview of AHS resources, with an emphasis on Heartworm Awareness Month. The June issues will feature the new AHS incidence map and survey.
- DVM360 was given exclusive permission to use the video interviews taped with presenters at the 2016 Triennial Symposium. These video interviews have been promoted online throughout the spring.

NEWS FROM THE AHS BOARD MEETING

The AHS Executive Board met March 12–14 in Atlanta for a strategic planning meeting and set the following priorities for the upcoming year.

- **Research** Sponsoring heartworm research will continue to be a priority.
- **Continuing Education** Practitioner education will also be a priority, but in the future, greater emphasis will be put on Heartworm University, which provides half-day educational programs at state and regional veterinary meetings, versus a half-day national

symposium at NAVC. The reason: due to the high cost of national symposia, Heartworm University enables the AHS to reach more practitioners with programming that can be tailored to their educational needs.

- **AHS Website** Updating the AHS website to better differentiate consumer from veterinary resources and to categorize materials by focus (prevention, diagnosis and treatment) and species will be undertaken over the next few months. The “heartworm basics” page continues to be the most-visited page on the website, followed by veterinary assets including the canine and feline heartworm guidelines and the AHS heartworm incidence maps.
- **Client Education Resources** The AHS will also continue developing fresh consumer education resources targeted toward consumers who are veterinary clients but have not yet been persuaded to provide year-round heartworm prevention for their pets. By addressing the various barriers (cost, convenience, appreciation of the risk, etc.) that have kept them from providing optimal protection, the goal is to “tip” them toward the desired behavior.
- **Guidelines** The AHS Guidelines on heartworm prevention, diagnosis, and treatment continue to be one of the most used resources from the Society. The Board has decided to hold off on making substantive changes to the AHS guidelines until the proceedings from the 15th Triennial Symposium is published in *Parasites and Vectors* later this year.
- **Transport Policy** AHS is also working with ASV to develop best practices guidelines for minimizing heartworm transmission in transported dogs. Watch for more information in the coming months and in the September issue of the Bulletin. ■

CLIENT EDUCATION

Newly Revised Feline Brochure Now Available! ORDER HEARTWORM CLIENT EDUCATION BROCHURES FOR YOUR PRACTICE

- Heartworm Disease in Dogs
- Heartworm Disease in Cats—*Newly revised!*
- Also available: **Prevention vs Treatment: The Truth About Heartworm Disease and Your Pet**

Printed brochures can be ordered in bundles of 100 copies.

For prices and shipping information please go to Veterinary Resources at heartwormsociety.org.



TRANSLATIONS OF THE AHS CANINE AND FELINE GUIDELINES ARE NOW AVAILABLE!

Coming Soon: Traditional Chinese and Simplified Chinese Translations of the Canine Guidelines!

Go to heartwormsociety.org now to download these free searchable PDF files:

- The **Canine Guidelines** in Spanish, French, Italian, and Portuguese
- The **Feline Guidelines** in Spanish, French, and Italian



Advantage Multi® for Dogs and for Cats

(imidacloprid + moxidectin)

BRIEF SUMMARY: Before using Advantage Multi® for Dogs (imidacloprid+moxidectin) or Advantage Multi® for Cats (imidacloprid +moxidectin), please consult the product insert, a summary of which follows:

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

Advantage Multi for Dogs:

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 the application sites for two (2) hours after application.

(See Contraindications, Warnings, Human Warnings, and Adverse Reactions for more information.)

INDICATIONS:

Advantage 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. Advantage Multi for Dogs kills adult fleas and is indicated for the treatment of flea infestations (*Ctenocephalides felis*). Advantage Multi for Dogs is indicated for the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei var. canis*. Advantage Multi for Dogs is also indicated for the treatment and control of the following intestinal parasites species: Hookworms (*Ancylostoma caninum*) (*Uncinaria stenocephala*), Roundworms (*Toxocara canis*) (*Toxascaris leonina*) and Whipworms (*Trichuris vulpis*).

Advantage Multi for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. Advantage Multi for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. Advantage Multi for Cats is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the intestinal parasites species Hookworm (*Ancylostoma tubaeforme*) and Roundworm (*Toxocara cati*). **Ferrets:** Advantage Multi for Cats is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. Advantage Multi for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations in ferrets.

CONTRAINDICATIONS: Do not administer this product orally. (See WARNINGS). Do not use the Dog product (containing 2.5% moxidectin) on Cats.

WARNINGS:

Advantage Multi for Dogs: For the first 30 minutes after application: Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs, and 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.

Advantage Multi for Cats: Do not use on sick, debilitated, or underweight cats. Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight. Do not use on sick or debilitated ferrets.

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. Dogs: Children should not come in contact with the application sites for two (2) hours after application. Cats: 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. 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 product with caution. In case of an 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 Material Safety Data Sheet (MSDS) provides additional occupational safety information. For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

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 Advantage Multi for Dogs has not been established in breeding, pregnant, or lactating dogs. The safe use of Advantage Multi for Dogs has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight. Advantage Multi for Dogs has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

Cats may experience hypersalivation, tremors, vomiting and decreased appetite if Advantage Multi for Cats is inadvertently administered orally or through grooming/licking of the application site. The safety of Advantage Multi for Cats has not been established in breeding, pregnant, or lactating cats. Use of this product in geriatric cats with subclinical conditions has not been adequately studied. Ferrets: The safety of Advantage Multi for Cats has not been established in breeding, pregnant, and lactating ferrets. Treatment of ferrets weighing less than 2.0 lbs. (0.9kg) should be based on a risk-benefit assessment. The effectiveness of Advantage Multi for Cats in ferrets weighing over 4.4 lbs. (2.0 kg) has not been established.

ADVERSE REACTIONS: Heartworm Negative Dogs: the most common adverse reactions observed during field studies were pruritus, residue, medicinal odor, lethargy, inappetence and hyperactivity. **Heartworm Positive Dogs:** the most common adverse reactions observed during field studies were cough, lethargy, vomiting, diarrhea, (including hemorrhagic), and inappetence. **Cats:** The most common adverse reactions observed during field studies were lethargy, behavioral changes, discomfort, hypersalivation, polydipsia and coughing and gagging. **Ferrets:** the most common adverse reactions observed during field studies were pruritus/scratching, scabbing, redness, wounds and inflammation at the treatment site, lethargy and chemical odor.

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

Advantage Multi is protected by one or more of the following U.S. patents: 6,232,328 and 6,001,858.

NADA 141-251,141-254 Approved by FDA

18726

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Cats only
- FLEAS | HEARTWORMS

See the difference at bayerdvm.com/multi

*Based on label indications: spectrum of species, parasites (dog) and life stages (dog and cat).
†Advantage Multi® for Cats (imidacloprid + moxidectin) (0.4 mL) is indicated for ferrets that weigh at least 2 lbs.

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Dogs (imidacloprid + moxidectin) to use by or on the order of a licensed veterinarian. **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 the application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings, and Adverse Reactions, for more information.) **CONTRAINDICATIONS:** Do not use this product on cats.

CAUTION: Federal (U.S.A.) law restricts Advantage Multi® for Cats to use by or on the order of a licensed veterinarian. **WARNINGS:** Do not use on sick or debilitated cats or ferrets. Do not use on underweight cats. (see ADVERSE REACTIONS); Do not use on cats less than 9 weeks of age or less than 2 lbs body weight. Do not use on ferrets less than 2 lbs body weight. **PRECAUTIONS:** Avoid oral ingestion. **HUMAN WARNINGS:** Children should not come in contact with the application site for 30 minutes after application.