Putting heartworm disease behind you.
The journey to recovery starts here.
What is heartworm disease?
Heartworm disease is caused when an infected mosquito transfers heartworms from one animal to the next. Foot-long worms can thrive near the heart and lungs, causing severe damage to an infected dog. Treatment for heartworm disease should be administered as early in the course of the disease as possible.¹

**THE HEARTWORM LIFECYCLE**

Within seven months, adult female heartworms release young heartworms into the dog’s bloodstream.

A mosquito bites an infected animal and takes in young heartworms as it feeds.

Heartworms grow in the mosquito and become infective.

When an infected mosquito bites another dog, the heartworms enter through the bite wound.

Inside the dog, heartworms grow into adults that live in the major vessels around the heart and, in severe cases, the heart itself.

Your dog has been diagnosed. What’s next?
Every case of heartworm disease is different. Your veterinarian will develop a treatment plan specifically for your dog and advise you on aftercare.

**TIPS ON GETTING THROUGH TREATMENT**
From the first dose of DIROBAN until 6–8 weeks after treatment concludes, it will be essential to keep your dog calm.³ That means kenneling your dog most of the time and using a leash when going outside. The American Heartworm Society offers further guidance⁵ on making it through the period of restricted activity during heartworm treatment:

- **Replace activity with affection.** Snuggle up while you’re online, reading or watching TV.
- **Keep your dog away from visitors** and even windows—if he barks at outside activity.
- **Stretch out meal times.** Put part of your dog’s daily food portion in hollow chew toys or “puzzle feeders” so that your dog will spend hours extracting food or treats from them.
- **Give him things to chew.** A bored dog is sometimes a destructive dog. Durable chew toys can channel this behavior and help keep your confined dog happily occupied.

**POST-TREATMENT**
About 6 months after the final DIROBAN treatment, your veterinarian will perform a follow-up test to confirm all heartworms have been killed.

**Life after heartworm disease**
After heartworm treatment, it’s natural to be highly aware and concerned about the risk of your dog becoming infected again. Talk with your veterinarian about protecting your best friend with year-round heartworm disease prevention.

For more information and support, go to Diroban.com.
A heartworm-positive diagnosis is devastating news, but there is hope. That’s because most dogs can be successfully treated. The sooner adult and immature worms are killed, the greater your dog’s chances of getting back to chasing balls and making new friends at the park.

**RECOMMENDED FOR A REASON**

With DIROBAN™ (melarsomine dihydrochloride), your dog returns to being himself again much sooner.

Melarsomine dihydrochloride, the active ingredient in DIROBAN, is the only treatment for canine heartworm disease recommended by the American Heartworm Society. It results in a shorter recovery time than the alternative treatment, which can last up to 2 years.

The longer heartworms live in your dog, the more damage they can do.

**We’re here to help you and your dog through heartworm treatment.**

**LEARN MORE ABOUT:**
- What causes heartworm disease
- Signs and symptoms
- Details about treatments
- Care during and after treatment

Please visit **Diroban.com** for more tips and advice on how to make the journey back to health as easy as possible for both you and your best friend.

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**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 Prescribing Information for additional safety information and precautions on the following page.

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Canine Heartworm Treatment

**INDICATIONS**

The exact mode of action on *D. immitis* is unknown.

**PHARMACOLOGY**

Melarsomine dihydrochloride is an organic arsenical chemotherapeutic agent. Melarsomine has a molecular weight of 301.34 and is chemically designated as 4-[(4,6-diamino-1,3,5-triazin-2-yl)amino]phenylthioarsanate of dihydrochloride. It is freely soluble in water. When injected intramuscularly, it is rapidly absorbed. The exact mode of action on *D. immitis* is unknown.

**INDICATIONS**

DIROBAN Sterile Powder for Injection is indicated for the treatment of stabilized Class 3, 2nd, and 3rd 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 enrolled in 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. Patients with mild disease may have subjective signs such as 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+), mild peripheral edema (1+), and or radiologic signs of right heart failure (diagnostic criteria, a pulmonary arterial diameter >17 mm, >20% collapse of the right main pulmonary artery) may be present. Radiographic signs may include right ventricular enlargement, slightly enlarged pulmonary arterial diameter, or irregularly shaped or very opaque vessels. Patients may be free of subjective clinical signs or may have a general loss of condition or 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, right ventricular enlargement, or radiographic evidence of right heart failure such as ascites and/or jugular pulse. Radiographic signs may include right ventricular enlargement or right atrial enlargement, severe pulmonary artery enlargement, increased pulmonary vascularity, and foci of normal and diffused 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 abnormalities. These dogs may have radiographic or other signs of heart failure or radiographic signs of thromboembolism, but they may have no subjective signs of heart failure or pulmonary arterial disease. These patients have a guarded prognosis. Subjective signs of disease may include cardiac cachexia, right ventricular enlargement, decreased peripheral perfusion, or evidence of right heart failure such as ascites and/or jugular pulse. If radiographic signs of heart failure or thromboembolism are present, these patients have a guarded prognosis.
the average duration of each event, as calculated from the 311 dogs treated with melarsomine dihydrochloride in the clinical trial fields.

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

<table>
<thead>
<tr>
<th>Clinical Observation/ Adverse Reaction</th>
<th>Average Onset Time in Days (range)*</th>
<th>Average Duration in Days (range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling/Edema/Seroma Pain/Discomfort/ Inflammation/Head Deformity</td>
<td>6 (0-77)</td>
<td>18 (&lt; 1-210)</td>
</tr>
<tr>
<td></td>
<td>1 (0-6)</td>
<td>2.5 (1-30)</td>
</tr>
<tr>
<td>Generalized/Local Myalgia with Tenderness and Stiffness</td>
<td>3 (1-8)</td>
<td>9 (&lt; 1-30)</td>
</tr>
<tr>
<td>Persistent (lumps, knots, nodules, masses)</td>
<td>22 (0-99)</td>
<td>47 (&lt; 1-152)</td>
</tr>
<tr>
<td>Abscess (sterile and septic)</td>
<td>24 (10-42)</td>
<td>21 (5-56)</td>
</tr>
<tr>
<td>Coughing/Gagging</td>
<td>10 (1-103)</td>
<td>13 (&lt; 1-154)</td>
</tr>
<tr>
<td>Depression/Lethargy</td>
<td>5 (0-48)</td>
<td>6 (&lt; 1-48)</td>
</tr>
<tr>
<td>Anorexia/Inappetence</td>
<td>5 (0-63)</td>
<td>10 (&lt; 1-134)</td>
</tr>
</tbody>
</table>

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

### Mortality in Dogs with Class 1, 2, and 3 Heartworm Disease Treated with melarsomine dihydrochloride in Clinical Field Trials

<table>
<thead>
<tr>
<th>CLASS 1, 2 % OF DOGS (n=267)</th>
<th>CLASS 3 % OF DOGS (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Deaths</td>
<td>5.2</td>
</tr>
<tr>
<td>Cause:</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>2.3</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>0.0</td>
</tr>
<tr>
<td>Euthanasia (unrelated to treatment or underlying disease)</td>
<td>1.1</td>
</tr>
<tr>
<td>Euthanasia (related to treatment or underlying disease)</td>
<td>0.0</td>
</tr>
<tr>
<td>Underlying Disease</td>
<td>0.8</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1.1</td>
</tr>
</tbody>
</table>

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, hypoesthesia, 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 parasyis and paralysis in dogs following administration of melarsomine dihydrochloride. To report a suspected adverse reaction, contact Zoetis Inc. at 1-866-963-4636.

### 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. BAL in Oil Ampules (Dimicorpal injection, USP) [Akorn, San Clemente, California, at 1-800-225-9851] 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.

### EFFICACY

Results of the laboratory and clinical field trials demonstrate that treatment with melarsomine dihydrochloride is effective in reducing and/or clearing D. immitis infections in dogs with Class 1, 2, and 3 heartworm disease. Evaluations for efficacy were determined by post-mortem worm counts in the laboratory studies and detection of antigen in the blood and subjective clinical assessments in the clinical trials. Physical exams, assessments of clinical variables, class of heartworm disease, radiographic examinations, as well as complete blood counts, serum chemistry profiles, and urinalysis were evaluated in the field trials.

### Laboratory Studies

In placebo-controlled laboratory studies, melarsomine dihydrochloride, administered at 2.5 mg/kg twice, 24 hours apart, was 90.7% effective against transplanted adult heartworms and 90.8% effective against induced infections of 4 month old (L₄) immature heartworms. To evaluate the effectiveness of the alternate dosing regimen, dogs with transplanted heartworms were treated with either 2.5 mg/kg once or 2.5 mg/kg every 24 hours apart for 1 month followed with 2.5 mg/kg administered twice 24 hours apart. A single injection of melarsomine dihydrochloride at 2.5 mg/kg reduced male worms 87.7% and female worms 16.9% (total 51.7%). When the full regime was used 100% of male worms and 98% of female worms were killed (total 99%). Dogs with natural D. immitis infections were treated with melarsomine dihydrochloride at 2.5 mg/kg twice, 24 hours apart. This dose was repeated and diarrhea were seen in the second dog within 24 hours of injection. The dog vomited and 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.

### ANADA 200-609, Approved by FDA

Diroban should be administered by deep intramuscular injection only in the epaxial (lumbar) muscles in the third through fifth lumbar region (see graphic). Do NOT ADMINISTER AT ANY OTHER SITE. Avoid superficial injection or leakage. Use a 23 gauge 1 inch needle for dogs equal to or less than 10 kg (22 lb) in weight. Use a 22 gauge 1/2 inch needle for dogs greater than 10 kg (22 lb). Use alternating sides with each administration, if repeated administrations are warranted avoid injecting at the same lumbar location. Record the location of the first injection(s) in the patient’s medical record for future reference.

### Disease Classification

It is vital to classify the severity of heartworm disease to apply the appropriate dosage regime for DIROBAN (see INDICATIONS).

#### Class 1 and 2

If necessary, dogs should be stabilized prior to treatment. DIROBAN should be administered intramuscularly in the lumbar (L₄-L₅) muscles at a dose of 2.5 mg/kg twice, 24 hours apart (see Dosing Table). Four months following treatment, a second treatment series (2.5 mg/kg twice, 24 hours apart) can be elected taking into consideration the response to the first DIROBAN treatment and the condition, age, and use of the dog. Worms that were too young to be killed by the first treatment series, i.e., < 4 months, may be killed by a second treatment series.

#### Class 3:

Alternate Dosing Regime: Dogs with severe (Class 3) heartworm disease should be stabilized prior to treatment and then dosed intramuscularly in the lumbar (L₄-L₅) muscles with a single injection of 2.5 mg/kg then approximately 1 month later with 2.5 mg/kg administered twice 24 hours apart (see Dosing Table). Dosing Table: Care must be taken to administer the proper dose. Accurately weigh the dog and calculate the volume to be injected based on the dose of 2.5 mg/kg (11 mg/lb). This is equivalent to 0.1 mL/kg (0.045 mL/kg). The following table should be used as a guide to ensure that the proper volume has been calculated.

<table>
<thead>
<tr>
<th>WEIGHT (lb)</th>
<th>2.2</th>
<th>4.4</th>
<th>6.6</th>
<th>8.8</th>
<th>11</th>
<th>13.2</th>
<th>15.4</th>
<th>17.6</th>
<th>19.8</th>
<th>22</th>
<th>44</th>
<th>66</th>
<th>88</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOLUME PER INJECTION (mL)</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
<td>2.0</td>
<td>3.0</td>
<td>4.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

### Treatment Response

A baseline can be established pre-treatment by using commercially available in-office heartworm antigen test kits prior to treatment. Treatment response can be assessed best by heartworm antigen testing applied 4 months after treatment. A successful treatment is determined to be conversion from an antigen positive to an antigen negative status. In dogs with signs of heartworm disease, gradual improvement should be observed as the long-term effects of the heartworm infection resolve. Some dogs may have chronic effects that will not resolve.

### CONCOMITANT THERAPY

During the course of clinical field trials, DIROBAN was administered concurrently with anti-inflammatories, antibiotics, insecticides, heartworm prophylactics, and various other drugs commonly used to stabilize and support dogs with heartworm disease with no adverse drug interactions noted.

### Routine Prophylaxis

If the dog is not currently receiving commercially available heartworm preventative, they may be administered consistent with label recommendations and re-exposure risk.

### STORAGE CONDITIONS

Store upright at controlled room temperature (20°- 25°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 lophylomized melarsomine dihydrochloride with accompanying 5 - 2 mL vials of sterile water for injection.

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007
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