DIROBAN Sterile Powder for Injection

Canine Heartworm Treatment

DIROBAN Sterile Powder for Injection is indicated for the treatment of stabilized Class 1a, D. immitis 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 3a, 2b, and 3c heartworm disease caused by immature (4 month-old, stage L5) to mature adult infections of Dirofilaria immitis in dogs.

Heartworm Disease Classification: The following parameters were used to classify the dogs into clinical 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 in 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+) may be present. Radiographic signs may include right ventricular enlargement, slight pulmonary artery enlargement, or circumscribed peripheral 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 congestive failure (wasting, weight loss, poor coat, 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, and circumscribed 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 changes consistent with those described for moderate disease (Radiographic changes 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 Caudal Syndrome (L. immitis present in the vena cavae and right atrium).

WARNING

DIROBAN should be administered as a deep intramuscular injection ONLY in the epaxial (lumbar) muscles (L1-L3). DO NOT USE IN ANY OTHER MUSCLE GROUP. DO NOT USE INTRAVENTRALLY. Care should be taken to avoid superficial injection or leakage (see SAFETY).

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 anticoagulant therapy due to thromboembolism associated with the administration of the drug 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.

SAFETY

Melarsomine dihydrochloride has a low margin of safety. A single dose of 7.5 mg/kg (3X the recommended dose) can result in pulmonary inflammation, edema, and death. Daily administration of 2X and 3X the recommended dose for 6 days caused no renal injury; however, daily administration of these doses for 14 days caused renal damage in some heartworm dogs. Adverse reactions, primarily at the injection sites, were seen at the recommended dose in clinical trials (see ADVERSE REACTIONS).

Studies in Healthy (Heartworm Negative) Dogs: The safety of melarsomine dihydrochloride was evaluated in 24 healthy beagle dogs. Drug was administered at 0, 2.5, 3.0, and 7.5 mg/kg for 6 consecutive days (0, 1, 2, and 3 times the recommended dosage). Clinical observations included tremors, lethargy, unsteadiness/ataxia, restlessness, panting, shallow and labored respiration, and/or rales. These signs were seen in all dogs treated with melarsomine dihydrochloride with frequency and intensity increasing with increasing dosage. Death or euthanasia in a moribund state occurred in 3/6 dogs in the 75 mg/kg (5X) group. The signs described in dogs, in addition to the signs described above, included collapse, collapse, severe salivation, vomiting, respiratory distress, cyanosis, stupor, and death within 4 hours of the first dose in two dogs and within 20 hours of the second dose in one dog.

Body weights, water consumption, hematology and urine parameters were comparable to control dogs. No alterations in blood consumption occurred in dogs for 2 to 5 days after dosing. Elevations, up to 25-fold, in creatinine kinase (CK) and elevations, up to 7-fold, in aspartate aminotransferase (AST) were observed and related grossly and histologically to muscle damage at the injection sites. Up to 2-fold elevations in alanine aminotransferase (ALT) were also noted. Gross and microscopic pathology revealed no organ-related toxicity other than edema and acute inflammation in the lungs and pleural effusion in the 3 dogs that died at the 75 mg/kg dose. Injection site lesions were observed in the skeletal muscles at all dose levels. At 5.0 mg/kg an injection site abscess was observed in one dog.

A separate study was conducted to examine the intensity and duration of injection site reactions. The dogs were dosed at 2.5 and 5.0 mg/kg (1X and 2X the recommended dose) twice 24 hours apart. This treatment sequence was repeated 4 months later. One group received the second treatment series after 1 month to mimic the alternate dosing regime. Swelling, which occurred in clinical trials for DIROBAN, was not observed in this study. Elevations of the same magnitude as in the previous study and again related to muscle damage were observed in CK and AST within 8 hours of injection. The values approached pretest levels by 72 hours and were within the normal range established by control animals by 1 month post-injection.

Gross and microscopic evidence of injection site irritation (cellular infiltrate, fibrosis, necrosis, and hemorrhage) was still evident in the muscles 1 month post-injection in dogs at both dose levels. By 3 months post-injection, resolution (healing) was evident microscopically in the skin and muscle at the 2.5 mg/kg dose level. One dog treated at the 20 mg/kg dose in the 2X dose group had extension of treatment-related injection site inflammation into deeper tissues (ie., abdominal cavity) as evidenced by an adhesion between the spleen and mesentry.

ADVERSE REACTIONS (SIDE EFFECTS)

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 sites. Though subjective in nature, these reactions were considered a normal part of the disease process. Onset and duration of clinical observations/Adverse Reactions are reported in Clinical Field Trials. The following table enumerates adverse events that occurred in 15% or more of dogs with Class 1, 2, and 3 heartworm disease treated with melarsomine dihydrochloride in clinical field trials. However, the occurrence of these reactions has no relationship to the reaction to the drug. Additional adverse reactions observed in clinical trials are presented thereafter.

Prevalence of Clinical Observation/Adverse Reactions Reported in Clinical Field Trials

Clinical Observation/Adverse Reaction % of dogs n=311 % of dogs n=63

Injection Site Reactions 73.2 3.8

Coughing/Gagging 19.2 14.3

Depression/Lethargy 7.6 15.4

Anorexia/Inappetence 5.8 3.2

Pyrexia 3.9 2.6

Lung Congestion/Sounds 11.2 0.0

Emesis 5.1 16.0

Diarrhea 2.6 0.0

Dyspnea 2.6 0.0

Hypersalivation 1.9 0.0

Tremors 1.9 0.0

Hemoptysis 0.0 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 icterus), melena, pancreatitis, renal failure, rectal hemorrhage, reticulocytosis, gastritis, hemolytic uremic syndrome, polypua, pyuria, bronchitis, miscellaneous respiratory organ disease, pneumonia, tachypnea, tracheobronchitis, wheezing, alopecia, hair color and coat character change, miscellaneous skin problem, ataxia, convulsion, seizures, septicemia, urinary 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
An open-label clinical field study was conducted in 44 dogs, 1.5 to 14 years old and weighing 3.2 to 50.0 kg, with stabilized, Class 3 heartworm disease. Dogs received the alternate dosing regime (2.5 mg/kg once followed 1 month later by 2.5 mg/kg twice 24 hours apart). The conversion rate was 89.2% 4 months after the final treatment. In a small, uncontrolled clinical trial (n=10) in Class 3 dogs the conversion rate was 100% 4 months after treatment.

**Dosage and Administration**

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 ADAPT DOSE 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 1½ 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.

**Mortality**

Death is a possible sequela 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 cause of death, if known.

<table>
<thead>
<tr>
<th>Cause</th>
<th>CLASS 1</th>
<th>CLASS 2</th>
<th>CLASS 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>2.3</td>
<td>2.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>0.0</td>
<td>4.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Euthanasia (unrelated)</td>
<td>1.1</td>
<td>0.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Euthanasia (related)</td>
<td>0.0</td>
<td>2.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Underlying Disease</td>
<td>0.8</td>
<td>2.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1.1</td>
<td>6.8</td>
<td>0.0</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, 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 paroxysms and paralyses in dogs following administration of melarsomine dihydrochloride. To report a suspected adverse reaction, contact Zoetis Inc. at 1-888-963-7421.

**Overdosage**

Three dogs were inadvertently overdosed with melarsomine dihydrochloride in the clinical field trials when the dose was calculated on a mg/kg basis rather than a mg/g/lb 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 10X 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 DEATH). BAL in Oil Ampules (Dimercaprol 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 results in reduction and/or clearance of *D. immitis* infection 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 (Lx) 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 twice followed 1 month later 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 4 months later. Antigen tests performed at month 4 showed a 90% conversion from antigen positive to antigen negative status. Worm counts at month 9 showed a 98.7% reduction in worm numbers as compared to placebo controls.

**Clinical Field Studies**

In two well-controlled field studies, 169 client-owned dogs, 1 to 12 years old and weighing 3.0 to 59.0 kg, with Class 1 or stabilized Class 2 heartworm disease were treated with melarsomine dihydrochloride. In-office blood antigen tests were used pretreatment to diagnose the *D. immitis* infection and 4 months after drug administration to assess treatment response. At month 4, 76.2% to 81% of the dogs had converted from antigen positive to antigen negative status. The conversion rate ranged from 89.7 to 98.2% after two treatment series. In an open-label study in 102 dogs, 1 to 18 years old and weighing 4.4 to 40.8 kg, with Class 1 or stabilized Class 2 heartworm disease, the conversion rate was 84% 4 months after one series of treatments. When a second series was given at month 4, the conversion rate was 94%.

**SAFETY**

During the course of clinical field trials, DIROBAN was administered concurrently with anti-inflammatories, antibiotics, insecticides, heartworm prophyllactic, 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 lyophilized melarsomine dihydrochloride with accompanying 5 - 2 mL vials of sterile water for injection.