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 healthy 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 studied in healthy beagle dogs. Drug was administered at 0, 2.5, 5.0, and 7.5 mg/kg for 6 consecutive daily doses (0.1 ml/kg of 2.5 mg/mL of active ingredient) in 2 injection series. Each injection site was observed for 3 months post-injection.

ADVERSE REACTIONS: The safety of melarsomine dihydrochloride was studied in 24 healthy beagle dogs. Drug was administered at 0, 2.5, 5.0, and 7.5 mg/kg for 6 consecutive days (0.1 ml/kg of 2.5 mg/mL of active ingredient) in 2 injection series. Each injection site was observed for 3 months post-injection.

Melarsomine dihydrochloride is an organic arsenical chemotherapeutic agent. Melarsomine has a molecular weight of 501.34 and is chemically designated as 4-[(4, 6-diamino-1, 3, 5- triazin-2-yl) amino] phenyldithioarsenite of di (2-aminoethyl), dihydrochloride. It is freely soluble in water. When injected intramuscularly, it is rapidly absorbed. The exact mode of action on the parasites is unknown.

INDICATIONS
DIROBAN Sterile Powder for Injection is indicated for the treatment of established Class I, II, and III heartworm disease caused by immature (4 month-old, stage L3) to mature adultJapanization 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. Patients in this category are at greater risk of significant anemia (PCV <20% or other hematologic abnormalities) may be present. Proteinuria patterns and diffuse patterns of pulmonary densities or radiographic signs of thromboembolism. Signs plus right atrial enlargement, severe pulmonary artery enlargement, circumscribed to chronic mixed signs associated with right heart failure such as ascites (melarsomine dihydrochloride may be present. 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.

Contraindications: DIROBAN is contraindicated in dogs with severe Class IV heartworm disease. Patients in this category have severe pulmonary arterial disease. Patients in this category may have 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, slight pulmonary artery enlargement, or circumscribed perivascular densities plus mixed alveolar/interstitial lesions. Patients may be free of subjective signs or disease or may have a general loss of condition, fatigue on exercise, or occasional cough. If necessary, patients should be stabilized prior to treatment. See PRECAUTIONS AND DOSAGE AND ADMINISTRATION.

Clinical observations/adverse reactions occurring in less than 1% of treated dogs may be considered minor. Adverse reactions occurring in more than 1% of treated dogs are considered major. Adverse reactions occurring in 1% to 10% of treated dogs are considered moderate. Adverse reactions occurring in 10% to 20% of treated dogs are considered severe. Adverse reactions occurring in more than 20% of treated dogs are considered life-threatening.

In the previous study, melarsomine dihydrochloride induced injection site reactions in clinical trials were predominantly of mild to mild heartworm disease.

Pharmacology: Melarsomine dihydrochloride is an organic arsenical chemotherapeutic agent. Melarsomine has a molecular weight of 501.34 and is chemically designated as 4-[(4, 6-diamino-1, 3, 5- triazin-2-yl) amino] phenyldithioarsenite of di (2-aminoethyl), dihydrochloride. It is freely soluble in water. When injected intramuscularly, it is rapidly absorbed. The exact mode of action on the parasites is unknown.

Active Ingredients: DIROBAN contains melarsomine dihydrochloride (melarsomine [melarsamine] dihydrochloride) in the clinical field trials. Swelling, which occurred within 7 days of injection and persisted from 1 to 72 days (average 50 days), was the most common clinical observation. A small, firm nodule in the lumbar region of one dog in the IX group appeared during the first month of the study and persisted for 41 days. Pain at or following injection 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 pretreatment levels by 72 hours and were within the normal range established by control animals 1 month post-injection.

General: For use in dogs only. Safety for use in breeding animals and lactating or pregnant bitches has not been determined.

Human WARNINGS: Keep out of reach of children. Avoid human exposure. Wash hands thoroughly after use of 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).

Melarsomine dihydrochloride contains melarsomine dihydrochloride (melarsamine dihydrochloride). DIROBAN does not contain melarsomine dihydrochloride in the clinical field trials. Clinical observations/adverse reactions occurring in less than 15% of the dogs treated with melarsomine dihydrochloride include: abdominal hemorrhage, abdominal pain, bloody stool/diarrhea, colitis, gingivitis, pancreatitis, anemia, DIC, hemoglobinuria, ocular (mucous membranes), discoloration urine, hematuria, associated urination, and specific granulate in severity and recovery occurred in 1 to 2 weeks. Swimming, which occurred within 7 days of injection and persisted from 1 to 72 weeks (average 50 days), was the most common clinical observation. A small, firm nodule in the lumbar region of one dog in the IX group appeared during the first month of the study and persisted for 41 days. Pain at or following injection 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 pretreatment levels by 72 hours and were within the normal range established by control animals 1 month post-injection.

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

DOSAGE AND ADMINISTRATION: DIROBAN should be administered by deep intramuscular injection in the epaxial (lumbar) muscle (L3-L4). DO NOT USE IN ANY OTHER MUSCLE GROUP. DO NOT USE INTRAVENOUSLY. Care should be taken to avoid superficial or local adverse reactions at the injection site. Adverse reactions associated with treatment in the clinical field trials.

SAFETY: The safety of melarsomine dihydrochloride was studied in healthy beagle dogs. Drug was administered at 0, 2.5, 5.0, and 7.5 mg/kg for 6 consecutive daily doses (0.1 ml/kg of 2.5 mg/mL of active ingredient) in 2 injection series. Each injection site was observed for 3 months post-injection.

Clinical observations/adverse reactions occurring in less than 15% of the dogs treated with melarsomine dihydrochloride include: abdominal hemorrhage, abdominal pain, bloody stool/diarrhea, colitis, gingivitis, pancreatitis, anemia, DIC, hemoglobinuria, ocular (mucous membranes), discoloration urine, hematuria, associated urination, and specific granulate in severity and recovery occurred in 1 to 2 weeks. Swimming, which occurred within 7 days of injection and persisted from 1 to 72 weeks (average 50 days), was the most common clinical observation. A small, firm nodule in the lumbar region of one dog in the IX group appeared during the first month of the study and persisted for 41 days. Pain at or following injection 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 pretreatment levels by 72 hours and were within the normal range established by control animals 1 month post-injection.

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Prevalence of Clinical Observations/Adverse Reactions Reported in Clinical Field Trials: The following table enumerates adverse events that occurred in 15% or more of dogs with Class I, 2, and III 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 adverse reactions/adverse reactions seen in dogs treated with melarsomine dihydrochloride may be considered attributable to the drug or they may be secondary to worm death and/or the underlying heartworm disease process.
In 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 regimen (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 field trial (n=10) in Class 3 dogs the conversion rate was 100% 4 months after treatment.

**DOSAGE AND ADMINISTRATION**

DIROBAN should be administered only by deep intramuscular injection in the epaxial (lumbar) muscles in the third and fifth lumbar region (see graphic). DO NOT ADMINISTER AT ANY OTHER SITE. Avoid superficial injection or leakage. Use a 22 gauge 1 inch needle for dogs equal to or less than 10 kg (22 lb) in weight. Use a 22 gauge 1.5 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.

**SAFETY**

Onset times and durations of adverse reactions are descriptive and may vary. Onset times and durations are collected during clinical trials or clinical field trials and are based on the information available at the time of collection. To report suspected adverse drug events, for further technical assistance or to obtain a copy of the SDS, contact Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

**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/lb basis (2X overdose). 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 overdose. 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).

**CONCOMITANT THERAPY**

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* infections in dogs with Class 1, 2, and 3 heartworm disease. Evaluations for efficacy were determined to treatment and then dosed intramuscularly in the lumbar (L1-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). 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 (L1-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:**

Dose administration: 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/lb). The following table should be used as a guide to ensure that the proper volume has been calculated.

**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 (L1-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.

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| WEIGHT (lb) | 2.2 | 4.4 | 6.6 | 8.8 | 11 | 13.2 | 15.4 | 17.6 | 19.8 | 22 | 24 | 44 | 68 | 88 | 110 |
| WEIGHT (kg) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 20 | 30 | 40 | 50 |
| VOLUME PER INJECTION (mL) | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |

*Limited data were collected on the administration > 5.0 mL at a single injection site.

**Preparation:**

DIROBAN should be aseptically reconstituted only with the provided 2.0 mL of STERILE DILUENT (sterile water for injection). This provides 2.5 mg melarsomine dihydrochloride per 0.1 mL of injectable solution. Two 50 mg vials will be required for dogs weighing > 20 kg and 40 kg and 3 vials will be required for dogs > 40 kg and 60 kg. Use immediately. Reconstituted solution may be used within 36 hours if refrigerated and kept from light. Sterile water diluent is not suitable for intravenous injection.

**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 totally 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 lyophilized melarsomine dihydrochloride with accompanying 5 - 2 mL vials of sterile water for injection.

**Distributed by:**

Zoetis Inc.
Kalama, MI 49007

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