DIROBAN™

(melarsomine dihydrochloride)

Sterile Powder for Injection

Canine Heartworm Treatment

CAUTION : Federal 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 (L_3 - L_5).
DO NOT USE IN ANY OTHER MUSCLE GROUP. DO NOT USE INTRAVENOUSLY.
Care should be taken to avoid superficial injection or leakage (see SAFETY).

ACTIVE INGREDIENT
DIROBAN Sterile Powder for Injection contains 50.0 mg melarsomine dihydrochloride and 33.75 mg glycine USP. 1 vial: when reconstituted with the provided 2 mL of STERILE DILUENT (sterile water for injection) contains 25 mg/mL of active ingredient.

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- triazon-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 *D. immitis* is unknown.

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 L_5) 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. 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 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.

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 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 24 healthy beagle dogs. Drug was administered at 0, 2.5, 5.0, 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 groups 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 7.5 mg/kg (3X) group. The signs exhibited by these dogs, in addition to the signs described above, included 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 controls. Decreased food consumption occurred sporadically in the two high dose groups. 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 7.5 mg/kg dose. Injection site irritation was 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 series was repeated 4 months later. One group received the second treatment series after 1 month to mimic the alternate dosing regime. Swelling, which occurred within 7 days of injection and persisted from 1 to 72 days (average 30 days), was the most common clinical observation. A small, firm nodule in the lumbar region of one dog in the 1X 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 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 skeletal muscles at the 2.5 mg/kg dose level. One dog treated at the 2X dose had extension of treatment-related injection site inflammation into deeper tissues (i.e., abdominal cavity) as evidenced by an adhesion between the spleen and mesentery.

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