IMMITICIDE® Sterile Powder
(melarsomine dihydrochloride)

Approved by FDA under NADA # 141-042

CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

WARNING

IMMITICIDE® should be administered by deep intramuscular injection in the lumbar (epaxial) muscles (L3 – L5) ONLY.

DO NOT USE IN OTHER MUSCLE GROUP. DO NOT USE INTRAVENOUSLY.

Care should be taken to avoid superficial injection or leakage. (See SAFETY).

ACTIVE INGREDIENT

IMMITICIDE Sterile Powder contains 50.0 mg melarsomine dihydrochloride and 33.75 mg glycine USP, 1:val 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]phenoxy}diethylamine 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

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

Heartworm Disease Classification: The following parameters were used to classify the dogs in the clinical trials for IMMITECIDE. 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.

- Class 1: Patients in this category are characterized as having asymptomatic to mild heartworm disease. 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.

- 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 vascular changes plus mild 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.

- 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 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 administered the alternate dosing regime (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

IMMITICIDE is contraindicated in dogs with very severe (Class 4) heartworm disease. Patients in this category have Cavall Syndrome (D. immitis present in the venae cavea 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 an SDS or for assistance, contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251.

PRECAUTIONS

General: All dogs, with heartworm disease are at risk for post-treatment pulmonary thromboembolism (death of worms within the lungs) and resultant in fever, weakness, and coughing), though dogs with severe pulmonary artery disease have an increased risk and may exhibit more severe signs (diabetes, hemoptysis, right heart failure and possibly death). Dogs should be restricted from light to heavy exercise and restricted from 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 associated with thromboembolism, and/or progression of the underlying disease may be reduced to 10 to 20% of the Class 3 patients treated with IMMITECIDE (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, expected increase 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

IMMITICIDE 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 these doses for 14 days caused renal damage in healthy dogs. Adverse reactions, primarily at the injection sites, were noted at the recommended dose in 1 and 2X trials (see ADVERSE REACTIONS).

Studies in Healthy (Heartworm Negative) Dogs: The safety of IMMITECIDE 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 and 2 times the recommended dosage). Clinical observations included tremors, lethargy, unresponsiveness, ataxia, restlessness, panting, and shallow and labored respiration, and/or rectal temperature. All of these signs were in all groups treated with IMMITECIDE with frequency and intensity increasing with increasing dosage. Death or euthanasia in a montane blood state 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. Daily body weight gain was 50% greater in the 3X group than in the 2X group. Clinical signs, 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 pathologic changes were related to muscle damage at the injection sites. The dogs were administered 10 mg/kg (3X the recommended) as a single dose on post-treatment mortality due to thromboembolism, and/or progression of the underlying disease may occur in 10 to 20% of dogs treated. Patients in Class 3 should be stabilized prior to treatment and then administered the alternate dosing regime. Post-treatment mortality associated with thromboembolism (See DOSAGE AND ADMINISTRATION). Post-treatment mortality associated with thromboembolism, and/or progression of the underlying disease may be reduced to 10 to 20% of the Class 3 patients treated with IMMITECIDE (see Mortality). Hospitalization post-treatment and strict exercise restriction are recommended. Other supportive therapies should be considered on a case-by-case basis.

ADVERSE REACTIONS (Side Effects)

Injection Sites: All adverse reactions in the 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 to 2 weeks, severe reactions were noted in 1 to 1.5% of dogs 1X to 2X dosage. 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 injection sites 8 hours post-injection and 48 hours post-injection. Mild proteinuria (2+) was observed in 2 dogs at each dose level. (See ADVERSE REACTIONS)

Prevalence of Clinical Observations/Adverse Reactions Reported in Clinical Field Trials:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMMITECIDE</th>
<th>PLACEBO</th>
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<tbody>
<tr>
<td>n=311</td>
<td>n=63</td>
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</tr>
<tr>
<td>Injection Site Reactions</td>
<td>32.8</td>
<td>3.2</td>
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<tr>
<td>Coughing/Gagging</td>
<td>22.2</td>
<td>14.3</td>
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<tr>
<td>Depression/Lethargy</td>
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<tr>
<td>Anorexia/Inappetence</td>
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<td>Pyrexia (fever)</td>
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<tr>
<td>Lung Congestion/Sounds</td>
<td>5.5</td>
<td>1.6</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Hemoptysis</td>
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</table>

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

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Worm counts at month 9 showed a 98.7% reduction in worm numbers as compared to placebo controls. 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 to be conversion from an antigen positive to an antigen negative status. In dogs with signs of heartworm infection resolve. Some dogs may have chronic effects that will not totally resolve. A zero indicates that the reaction first occurred on the day of treatment.

**Clinical Field Studies:** In two well-controlled field studies, 169 client-owned dogs, 1 to 12 years old and weighing 2.2 to 40 kg, with Class 1 or stabilized Class 2 heartworm disease were treated with the recommended dose of IMMITICIDE. In-office blood antigen tests were used pre-treatment to diagnose the D. immitis infection and 4 months after drug administration to assess treatment response. At month 4, 76.2% 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. 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%. 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 regimens (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.

**DOSE AND ADMINISTRATION**

IMMITICIDE should be administered only by deep intramuscular injection in the epaxial (lumar) 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 1/2 inch needle for dogs greater than 10 kg (22 lb). Use alternating sides with each administration. If repeated administrations are warranted avoid injection at the same lumbar location. Record the date 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 regimen for IMMITICIDE. (See INDICATIONS).