MELARSOMINE Veterinary—Systemic

A commonly used *brand name* for a veterinary-labeled product is *Immi-ticide.*[R-1; 2]

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* section(s).

Category: Anthelmintic.

Indications

General considerations

Heartworm disease classification is used to categorize patients based on the severity of the disease. The treatment protocol is based on this classification.[R-1; 2]

Class 1: Asymptomatic to mild heartworm disease. General loss of condition, fatigue on exercise, or occasional cough may be present; however, radiographic and other laboratory tests are normal.[R-1; 2]

Class 2: Moderate heartworm disease. Abnormal radiographic signs or abnormal hematologic test results, such as anemia, are present. Radiographic signs include right ventricular enlargement, slight pulmonary artery enlargement, or circumscribed perivascular densities with mixed alveolar or interstitial lesions. For dogs in this class, anemia is defined as a packed cell volume (PCV) between 20 and 30%. Mild proteinuria (2+) may be present. General loss of condition, fatigue on exercise, or occasional cough may be present. Patients may need to be stabilized prior to treatment.[R-1; 2]

Class 3: Severe heartworm disease. Cardiac cachexia, constant fatigue, persistent cough, dyspnea, or other signs associated with right heart failure such as ascites or jugular pulse may be present. Radiographic signs may include right ventricular enlargement or right ventricular and right atrial enlargement, severe pulmonary artery enlargement, circumscribed to chronic mixed patterns and diffuse patterns of pulmonary densities or radiographic signs of thromboembolism. Significant anemia (PCV < 20%) or other hematologic abnormalitites may be present. Proteinuria (> 2+) may be present. Patients may have moderate clinical signs and significant laboratory or radiographic alterations or they may have significant clinical signs with only moderate laboratory and radiographic signs to be categorized as Class 3. Patients in Class 3 should be stabilized prior to treatment and then given the alternate dosing regimen. Patients in this class have a guarded prognosis.[R-1; 2]

Class 4: Severe heartworm disease. *D. immitis* is present in the venae cavae and right atrium (caval syndrome). Patients in this class should not be treated with melarsomine.[R-1; 2]

Accepted

Heartworm infection (treatment)—*Dogs:* Melarsomine is indicated in the treatment of heartworm infection caused by immature (4-month-old, fifth-stage larvae [L_5]) to mature adult infections of *D. immitis* in dogs with stabilized Class 1, 2, and 3 heartworm disease.[R-1; 2]

Regulatory Considerations

U.S. and Canada—

Federal law restricts melarsomine to use by or on the order of a licensed veterinarian.[R-1; 2]

Chemistry

Chemical group: Organic arsenical compound.[R-1; 2]

Chemical name: Melarsomine dihydrochloride—4-[(4,6-diamino-1,-3,5-triazon-2-yl)amino]phenyl-dithioarsenite of di(2-aminoethyl), dihydrochloride.[R-1; 2]

Molecular weight: Melarsomine dihydrochloride—501.34.[R-1; 2]

Solubility: Freely soluble in water[R-1; 2] and physiological saline.[R-9]

Pharmacology/Pharmacokinetics

Note: Arsenic was the substance measured in pharmacokinetic studies of melarsomine included in this monograph.[R-6]

Mechanism of action/Effect: The effects of injectable trivalent arsenicals on heartworms have not been completely defined but include alterations in glucose uptake and metabolism, inhibition of glutathione reductase, and alterations of the structure and function of the parasite's intestinal epithelium.[R-6]

Absorption: Rapidly absorbed after intramuscular administration.[R-1; 2] With intramuscular administration, the absorption half-life is 2.6 minutes.[R-11]

Distribution: *Dogs*—Volume of distribution: 0.73 ± 0.13 liter per kg (L/kg).[R-6]

Half-life: Elimination (terminal)—*Dogs:* 3.01 ± 0.96 hours.[R-6]

Peak serum concentration: *Dogs*—With an intramuscular dose of 2.5 mg/kg, a peak serum concentration of 0.59 ± 0.16 mcg/mL was reached at 10.7 ± 3.8 minutes.[R-6]

Mean residence time: *Dogs*—

Intramuscular administration of 2.5 mg/kg—2.56 ± 1.89 hours in plasma.[R-6]

Intravenous administration of 2.5 mg/kg—1 hour (central compartment); 6 hours (peripheral compartment).[R-6]

Elimination: *Dogs*—Total clearance: 2.68 ± 0.65 mL/min/kg.[R-6]

Precautions to Consider

Species sensitivity

Caution is advised if considering the use of melarsomine in animals other than dogs until species-specific information becomes available.

Otters and *pandas:* A red panda and two American river otters died within twenty-four hours of melarsomine administration as a treatment for *Dirofilaria* species infection. The dose given was 2.5 mg/kg, administered into the epaxial musculature, as recommended for dogs. The animals appeared to have died of acute pulmonary edema, perhaps due to melarsomine toxicity, anaphylaxis, or an idiosyncratic drug reaction.[R-5]

Pregnancy/Reproduction/Lactation

The safety of administering melarsomine to breeding, pregnant, or lactating dogs has not been determined.[R-1; 2]

Geriatrics

In clinical field trials, dogs 8 years of age or older experienced more post-treatment inappetence, lethargy, and vomiting than younger dogs.[R-1; 2]

Drug interactions and/or related problems

The following drug interations and/or related problems have been selected on the basis of their potential clinical significance:

Note: The manufacturer reports that no adverse drug interactions were noted during clinical field trials when melasomine was given concurrently with anti-inflammatory agents, antibiotics, insecticides, heartworm prophylactic medications, and other agents commonly used to stabilize dogs with heartworm

disease.[R-1; 2] However, drugs that may have adverse effects similar to those of melarsomine (e.g. depression, lethargy, inappetance, etc.) should be avoided to prevent synergy of adverse effects.

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]), serum,[R-1; 2] and Aspartate aminotransferase (AST [SGOT]), serum,[R-1; 2] and Creatinine kinase, serum (CK)[R-1; 2]

(values may be increased; administration of the recommended dose resulted in elevations of AST [SGOT, up to 7-fold] and CK [up to 25-fold] within 8 hours of injection, returning to near baseline levels within 72 hours of administration to healthy Beagle dogs; up to 2-fold elevations in ALT have been noted)[R-1; 2]

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problem exists:

» Heartworm disease, severe (Class 4; caval syndrome)[R-1; 2]

(surgical removal of adult worms from the right atrium and venae cavae with subsequent stabilization of the patient are required prior to treatment with melarsomine)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

» Body temperature and

» Respiratory rate and effort

(pyrexia, dyspnea, and cough may be signs of pulmonary thromboembolism; patients should be monitored by trained veterinary health care professionals during treatment and for up to 24 hours after the last injection)[R-1]

Heartworm antigen test

(treatment with melarsomine is considered successful if there is conversion to a negative antigen test 4 months after treatment)[R-1]

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Note: All dogs with heartworm disease are at risk for post-treatment pulmonary thromboembolism. Although melarsomine has demonstrated greater filaricidal efficacy than its predecessor, thiacetarsamide,[R-3; 4; 6] it has not been shown to increase the severity of pulmonary hypertension and pulmonary thromboembolism following therapy in manufacturer-sponsored, premarketing trials.[R-3; 6] If pulmonary thromboembolism does occur, clinical signs are generally noted 7 to 20 days after treatment.[R-1; 6] Dogs with severe pulmonary arterial disease have an increased risk and may exhibit more severe signs of pulmonary thromboembolism.[R-1; 2]

Adverse reactions observed after treatment with melarsomine may be directly attributable to the medication or may be secondary to worm death or the underlying heartworm disease process.[R-1] Adverse reactions following melarsomine administration may occur after the second injection in the series even if no problems were encountered with the first injection.[R-1; 2]

Those indicating need for medical attention

Incidence more frequent

Dogs

Anorexia or inappetence—13.2%;[R-1; 2; 6] ***coughing or gagging—***22.2%;[R-1; 2] ***injection site reaction—***32%;[R-1; 2] ***lethargy or depression—***15.4%[R-1; 2]

Note: While *coughing* or *gagging* occurred in 22.2% of dogs treated with melarsomine in a clinical trial, 14.3% of 63 heartworm-positive dogs given placebo also experienced coughing and gagging, presumably due to their heartworm disease.[R-1]

Injection site reactions occurred in approximately 30% of dogs treated with melarsomine in laboratory and field trials. While clinical recovery generally occurred within 1 week to 1 month, gross as well as microscopic evidence of injection site irritation was present 1 month after injection, with healing evident 3 months after injection.[R-1]

Incidence less frequent—1.5 to 10%[R-1; 2]

Dogs

Gastrointestinal effects (diarrhea, vomiting); ***hypersalivation; pyrexia; respiratory effects*** (dyspnea, hemoptysis, panting, pulmonary congestion)

Note: *Hypersalivation* and *panting* occurred infrequently in clinical trials; however, when seen, they generally occur within 30 minutes of injection and may be severe.[R-1] Panting, progressing to dyspnea, is the typical sign of overdose when two times the recommended dose has been administered.[R-7; 8]

Incidence rare—<1.5%[R-1; 2]

Dogs

Anemia; disseminated intravascular coagulation; fatigue; gastrointestinal effects (bloody diarrhea, colitis); ***gingivitis; hemoglobinemia; icterus; injection site reaction, severe; leukocytosis; neurologic effects*** (ataxia, convulsions, disorientation, restlessness); ***pancreatitis; respiratory effects*** (bronchitis, pneumonia, tachypnea, tracheobronchitis, wheezing); ***polydipsia/polyuria; urinary tract effects*** (discolored urine, hematuria, inappropriate urination, low urine specific gravity, pyuria); ***weight loss***

Note: One dog, treated at two times the recommended dose, was reported to experience a *severe injection site reaction* that involved extension of the inflammation from the injection site into the abdominal cavity, causing intra-abdominal adhesions.[R-1; 2]

Incidence unknown

Dogs

Paralysis; paresis[R-1]

Note: There have been rare reports of *paresis* or *paralysis* in association with intramuscular administration of melarsomine in the United States.[R-1] Cases have ranged from mild lameness in a hindlimb to more severe problems, such as marked paraparesis or paralysis.[R-10] In a few cases, progression from unilateral or bilateral hindlimb paralysis to deficits in all four limbs, coma, and death have occurred.[R-10] The pathogenesis of these effects is not well-defined; however, an adherence to the manufacturer's recommendations for injection technique is strongly recommended, out of concern that placement of the medication in or near sensitive structures may underlie these events.[R-10]

Those indicating need for medical attention only if they continue or are bothersome

Incidence rare—<1.5%

Dogs

Dermatologic effects (alopecia, hair color and coat character

change at injection site)[R-1; 2]

Overdose

For more information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer.**

General considerations

Melarsomine has a low margin of safety.[R-1; 2] A single dose of 7.5 mg per kg of body weight (mg/kg; 3 times the recommended dose) can result in pulmonary inflammation, edema, and death.[R-1; 2]

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs in parentheses where appropriate)—not necessarily inclusive:

Acute effects

Dogs

With a dose of 5 mg/kg a day for six days:[R-1; 2]

Diarrhea; fever; panting; restlessness; salivation; vomiting

With a dose of 7.5 mg/kg a day for six days:[R-1; 2]

Collapse; cyanosis; gastrointestinal effects (abdominal pain, diarrhea, vomiting);[R-6] ***lethargy; neurologic effects*** (ataxia, restlessness, stupor, tremors); ***respiratory effects*** (dyspnea, panting, rales, shallow and labored respiration); ***salivation; tachycardia***[R-6]

Note: Three of six dogs given melarsomine at a dose of 7.5 mg/kg died or were euthanized in a moribund state within two days of treatment.[R-1]

Chronic effects

Dogs

Nephrotoxicity—when administered at 2 or 3 times the recommended dose for 14 days[R-1; 2]

Treatment of overdose

Dimercaprol (BAL) Injection USP is reported to be an antidote for arsenic toxicity.[R-1; 2; 6] An intramuscular dose of 3 mg/kg, given within three hours, reduced the signs of toxicity associated with experimental administration of twice the labeled dose of melarsomine.[R-1; 2; 6; 11] Researchers performing the study repeated the dimercaprol dose once or twice, three hours apart.[R-6] In clinical situations, length of treatment with dimercaprol depends on the animal's response to treatment.

The efficacy of melarsomine may be reduced by coadministration with dimercaprol.[R-1; 2]

Client Consultation

In providing consultation, consider emphasizing the following selected information:

- Details of exercise restriction, including duration and level of limitation, based on severity of disease.
- Signs of pulmonary thromboembolism, including anorexia, coughing, dyspnea, fever, hemoptysis, lethargy, or tachypnea, and instructions to contact their veterinarian.

Veterinary Dosing Information

Melarsomine should be administered by deep intramuscular injection into the lumbar (epaxial) muscles only at the level of the third to fifth lumbar vertebrae [L3-L5], with special care taken to avoid superficial injection or leakage into superficial tissues.[R-1] For dogs weighing 10 kg or less, a 23-gauge, 1-inch needle should be used for intramuscular administration of the medication.[R-1] A 22-gauge, 1½-inch needle should be used for dogs weighing more than 10 kg.[R-1] Total doses exceeding a volume of 5 mL may be divided and administered in two sites, the second site approximately two lumbar vertebrae cranial to the initial site.[R-7] A new, sterile needle should be used at each administration site.[R-8] Melarsomine should not be administered intravenously.[R-1]

Class 1 and 2 dogs may have the treatment repeated four months after the initial treatment to kill worms that were too young (< 4 months) to be killed during the first treatment.[R-1] The decision to administer a second treatment series should be based on the response to the first melarsomine treatment and the condition, age, use of the dog, and the results of the heartworm antigen test.[R-1] In general, dogs with persistent positive heartworm antigen test results may require the second treatment series only if their clinical signs persist or if they are performance animals requiring optimal cardiac reserve. A careful risk-benefit assessment should be made on a case-by-case basis.[R-7]

Class 3 dogs should be stabilized and then treated according to the alternate dosing regimen to help decrease post-treatment mortality associated with thromboembolism.[R-1] 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 melarsomine.[R-1] Hospitalization after treatment and strict exercise restriction are recommended. Other supportive therapies should be considered on a case-by-case basis.[R-1]

If necessary, patients should be stabilized prior to treatment.[R-1]

All dogs should be observed during treatment and for twenty-four hours after the last injection.[R-1]

Exercise restriction, based on the severity of the heartworm disease, is generally recommended for 4 to 6 weeks following treatment to help prevent clinical signs of thromboembolism.

Parenteral Dosage Forms

MELARSOMINE DIHYDROCHLORIDE FOR INJECTION

Usual dose: Heartworm infection—*Dogs:*

For Class 1 and 2 patients: Intramuscular, 2.5 mg per kg of body weight, administered deeply into the lumbar (epaxial) muscles in the third to fifth lumbar vertebral region, avoiding superficial injection or leakage.[R-1; 2] The dose is repeated in twenty-four hours on the opposite side of the body.[R-1; 2]

Note: A large worm burden may increase the chances of post-treatment thromboembolism, even in Class 1 or 2 asymptomatic dogs; therefore, the alternate Class 3 treatment protocol may be considered for asymptomatic dogs with radiologic or serologic evidence of large worm burdens, and for dogs with inadequate medical histories adopted from areas where the incidence of heartworm disease is high.[R-7]

For Class 3 patients: Intramuscular, 2.5 mg per kg of body weight, administered deeply into the lumbar (epaxial) muscles in the third to fifth lumbar vertebral region, avoiding superficial injection or leakage.[R-1; 2] One month later, two additional doses of 2.5 mg per kg of body weight should be administered twenty-four hours apart, alternating sides of injection.[R-1; 2]

Note: The incidence of injection site reactions on the side receiving a second injection may be increased since the skeletal muscles at the first injection site may not have fully healed.[R-1; 2] If injection site swelling is present 1 month after the first treatment, the second injection may be delayed up to 1 month.[R-1; 2]

Strength(s) usually available: When reconstituted according to manufacturer's instructions—

U.S.:

Veterinary-labeled product(s):

25 mg melarsomine dihydrochloride per mL (Rx) [*Immiticide*].[R-1]

Canada:

Veterinary-labeled product(s):

25 mg melarsomine dihydrochloride per mL (Rx) [*Immiticide*].[R-2]

Packaging and storage: Prior to reconstitution, store upright at room temperature, preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer.[{R-1}]

Preparation of dosage form: Melarsomine should be aseptically reconstituted with 2 mL of sterile water for injection only.[{R-1}]

Caution:

Avoid human exposure and keep out of the reach of children.[{R-1; 2}]

Individuals administering this medication should either wear gloves or wash hands thoroughly after use.[{R-1; 2}]

If accidental human exposure occurs by any route (dermal, oral, or by injection), a physician should be consulted.[{R-1; 2}]

Melarsomine is potentially irritating to the eyes.[{R-1; 2}] If exposure occurs, eyes should be flushed with copious amounts of water.[{R-1; 2}]

Stability:

After reconstitution, melarsomine retains its potency for 24 hours if refrigerated, stored upright, and protected from light.[{R-1; 2}]

The reconstituted solution should not be frozen.[{R-1; 2}]

USP requirements: Not in USP.

Developed: 07/18/96
Revised: 02/26/02
Interim revision: 03/07/97; 05/14/97; 06/09/98; 12/01/08

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