ProHeart 6 (moxidectin)

Sustained Release Injectable for Dogs

CAUTION:

Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

ProHeart 6 (moxidectin) Sustained Release Injectable consists of two separate vials: one vial contains 10 mg moxidectin sterile microspheres and the second vial contains a specifically formulated sterile vehicle for constitution with the microspheres. No other diluent should be used. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 10 mg moxidectin, 3.1% glycerol triacetate, 2.4% hydroxypropyl cellulose, 3.1% glycolic acid, 0.17% sodium chloride, 0.17% methylparaben, 0.02% propylparaben and 0.001% butylated hydroxytoluene. Hydrochloric acid is used to adjust pH.

PHARMACOLOGY:

Moxidectin is a semi-synthetic methoxime derivative of nemadectin which is a fermentation product of Streptomyces cyanogenus. It has a high affinity for nematodes, including the larval and adult stages of Ancylostoma caninum and Uncinaria stenocephala. Moxidectin has a potency of 16 mg/kg in mice and 8 mg/kg in rats.

DOSAGE AND ADMINISTRATION:

Owners should be given the Client Information Sheet for ProHeart 6 to read before the drug is administered and should be advised to observe their dogs for potential drug toxicity described in the sheet.

In Frequent of Treatment: ProHeart 6 prevents infection by the first exposure to mosquitoes. Follow-up treatments may be given every six months if the dog has continued exposure to mosquitoes and the dog continues to be healthy without weight loss. When replacing another heartworm preventive product, ProHeart 6 should be given within one month of the last dose of the former medication.

Ancylostoma caninum larvae invade the tissues of the dog within 48 hours of exposure to infected mosquitoes. Therefore, the treatment interval for ProHeart 6 against A. caninum must be no longer than one month.

Dose: The recommended dose is 0.17 mg/kg (0.0773 mg/lb.). This amount of suspension will provide 0.17 mg moxidectin/kg bodyweight (0.0773 mg/lb.). To ensure accurate dosing, calculate each dose based on the dog’s weight at the time of treatment. Do not overdose growing puppies in anticipation of their expected adult weight. The following dosing chart may be used as a guide.

**Dosage Chart**

<table>
<thead>
<tr>
<th>Dog Wt. (lb)</th>
<th>Dose Volume (ml)</th>
<th>Dog Wt. (lb)</th>
<th>Dose Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.25</td>
<td>11</td>
<td>0.25</td>
</tr>
<tr>
<td>10</td>
<td>0.50</td>
<td>17</td>
<td>0.75</td>
</tr>
<tr>
<td>15</td>
<td>1.00</td>
<td>23</td>
<td>1.25</td>
</tr>
<tr>
<td>20</td>
<td>1.50</td>
<td>29</td>
<td>1.50</td>
</tr>
<tr>
<td>35</td>
<td>4.00</td>
<td>45</td>
<td>4.00</td>
</tr>
<tr>
<td>60</td>
<td>6.00</td>
<td>60</td>
<td>6.00</td>
</tr>
</tbody>
</table>

Injection Technique: The two-part sustained release product must be mixed at least 30 minutes prior to the intended time of use (see CONSTITUTION PROCEDURES for initial mixing instructions). Once constituted, swirl the bottle gently before every use to uniformly re-suspend the microspheres. Withdraw 0.05 mL of suspending/kg body weight into an appropriately sized syringe fitted with an 18G or 20G hypodermic needle. Doze among a single injection site. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

Using aseptic technique, inject the product subcutaneously in the left or right side of the neck. Do not inject this product intradermally. If administered subcutaneously, injection site reactions were visible grossly for up to 3 weeks after injection. Histologically, well-defined granulomatous reactions are observed. The reaction was not seen in dogs that received four injections in the same area on the neck and in one dog that received two injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous changes without signs of previous drug toxicity reactions. No adverse reactions were seen in dogs that received four injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous changes without signs of previous drug toxicity reactions. There were no reports of injection site reactions in these field studies and evaluations of the injection sites revealed no abnormalities.

In a laboratory safety study, ProHeart 6 was administered at 1, 3, and 5 times the recommended dose to 7- to 8-month-old dogs. Injection sites were not palpated to detect inflammation. All dogs treated with ProHeart 6 were evaluated before and after injection. Neurological examination performed at 1 month after injection revealed no abnormalities. In a laboratory safety study, ProHeart 6 was administered at 1.3 times the recommended dose in dogs with patent heartworm infections and up to 5 times the recommended dose in heartworm-positive collies did not cause any adverse reactions. ProHeart 6 administered at 3 times the recommended dose did not adversely affect the reproductive performance of male or female dogs. ProHeart 6 administered up to 3 times the recommended dose in 7-8-month-old puppies did not cause any systemic adverse effects.

In a well-controlled clinical field studies, ProHeart 6 was used in conjunction with a variety of veterinary products including antibiotics, anthelmintics, anti-inflammatory drugs, and non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics and fina control products.

Injection Site Reactions: Injection site observations were recorded during effectiveness and safety studies. In clinical studies, ProHeart 6 was administered at six-month intervals to client-owned dogs under field conditions. There were no reports of injection site reactions in these field studies and evaluations of the injection sites revealed no abnormalities.

A three-year repeated injection study was conducted to evaluate the safety of up to 6 injections of ProHeart 6 administered at the recommended dose (0.17 mg/kg) every 6 months. Mild erythema and localized subcuticular thickening were seen in some dogs that received the four injections in the same area on the neck and in one dog that received two injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous changes without signs of previous drug toxicity reactions. No adverse reactions were seen in dogs that received four injections in the same area on the neck. Microscopic evaluation on the injection sites from all dogs 6 months after the last injection consistently showed mild granulomatous changes without signs of previous drug toxicity reactions. The only adverse reaction seen that was not related to the injection site was weight loss in one dog. Some dogs treated with ProHeart 6 in laboratory effectiveness studies developed transient, localized inflammatory injection site reactions. These injection sites reactions were visible only for up to 3 weeks after injection. Histologically, well-defined granulomas were observed in some dogs at approximately 5 months after injection.

CONSTITUTION PROCEDURES:

The two-part ProHeart 6 product must be mixed at least 30 minutes prior to the intended time of use. Items needed to constitute ProHeart 6 include:

- Microspheres
- Vehicle
- Transfer needle (25G)
- Sterile 20 mL syringe for transfer

Constitution of the 20 mL vial product:

- 1 - Sterile vehicle - 17 mL/vial
- 5-Pack
- 11 - Moxidectin microspheres - 5 mg/vial
- 8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
- 9. Before every use, gently swirl the mixture to achieve uniform suspension.
- 10. Use a 3 mL or 5 mL syringe and an 18G or 20G needle for dosing. Dose immediately after drawing into dosing syringe. If administration is delayed, gently roll the dosing syringe prior to injection to maintain a uniform suspension and accurate dosing.

STORAGE INFORMATION:

Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After reconstitution, the constituted product remains stable for 4 weeks in a refrigerator. Avoid direct sunlight.

HOW SUPPLIED:

ProHeart 6 is available in the following three package sizes.

<table>
<thead>
<tr>
<th>Package</th>
<th>Vial Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-PACK</td>
<td>20 mL vial product</td>
</tr>
<tr>
<td>5-Pack</td>
<td>20 mL vial product</td>
</tr>
<tr>
<td>3-PACK</td>
<td>20 mL vial product</td>
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In a laboratory effectiveness study, dogs with 4- and 6-month-old heartworm infections experienced vomiting, lethargy and bloody diarrhea. These signs were more severe in the dogs with 4-month-old heartworm infections, including one dog that was unresponsive and required supportive care, than in the dogs with 6-month-old infections.

Post-Approval Experience (Rev. 2010)

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by system.

Immune: anaphylaxis and/or anaphylactoid reactions, urticaria, head/neck edema, pruritus, pale mucous membranes, convulsion, swallowing difficulty, shock, erythema, intradermal hematoxylin/eosinophilic, infiltrative, non-neutrophilic necrotizing fibroplasia (seen in reflected data). In other system categories could be related to allergic reactions, i.e., gastrointestinal, dermatologic, and hematologic.

Gastrointestinal: vomiting (with or without blood), diarrhea with or without blood, dysphagia

Hematological: depression, lethargy, anemia, fever, weight loss, weakness

Dermatological: pruritus/swelling, erythema multiforme

Neurological: seizures, ataxia, trembling, hind limb paresis

Cardiovascular: dyspnea, tachypnea, coughing

Hepatic: elevated liver enzymes, hyperbilirubinemia, hepatopathy

Urinary: elevated BUN, elevated creatinine, hematuria, polyuria, polydipsia

Cardiovascular: respiratory distress, dyspnea, cyanosis

Respiratory: dyspnea, tachypnea, coughing

Kidney: elevated liver enzymes, hypophosphatemia, hypocalcemia

Hepatomembrane: necrosis, liver, hepatitis, biliary stasis, polyuria, polydipsia

ProHeart 6 is not effective against adult D. immitis heartworms. ProHeart 6 is not effective against adult D. immitis heartworms. ProHeart 6 is not effective against adult D. immitis heartworms. ProHeart 6 is not effective against adult D. immitis heartworms. ProHeart 6 is not effective against adult D. immitis heartworms. ProHeart 6 is not effective against adult D. immitis heartworms.