RISK MINIMIZATION ACTION PLAN (RiskMAP) FOR:

PROHEART® 6 (moxidectin)
for extended-release injectable suspension
NADA 141-189
and
PROHEART® 12 (moxidectin)
for extended-release injectable suspension
NADA 141-519

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BACKGROUND

The purpose of this Risk Minimization Action Plan (RiskMAP) is to ensure the safe and effective use of ProHeart 6 (moxidectin) for extended-release injectable suspension for use in dogs and ProHeart 12 (moxidectin) for extended-release injectable suspension for use in dogs, with the aim of achieving maximum benefits of heartworm prevention while minimizing risks to dogs. This risk mitigation strategy utilizes a number of tools including client and veterinary education and adverse drug experience (ADE) monitoring.

ProHeart 6 and ProHeart 12 are each approved for the prevention of heartworm disease caused by *Dirofilaria immitis*, and treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infection. Both products contain the same moxidectin microspheres and have similar safety profiles. The differences between the products include:

- ProHeart 12 contains 3 times the dose of moxidectin microspheres in ProHeart 6.
- ProHeart 6 is for use in dogs 6 months of age or older while ProHeart 12 is for use in dogs 12 months of age or older.
- ProHeart 6 has a 6-month duration of effectiveness while ProHeart 12 has a 12-month duration of effectiveness.

In 2004, at the request of the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM), Fort Dodge Animal Health (FDAH) voluntarily recalled ProHeart 6 because of CVM's concerns regarding reports of serious ADEs in dogs following use of the drug. Signals of concern to CVM included anaphylaxis, liver disease, autoimmune hemolytic disease, seizures, and death.

In response to the Agency's concerns, and following recommendations from the January 31, 2005, Veterinary Medicine Advisory Committee (VMAC) meeting[1], FDAH conducted studies to further evaluate the safety profile of ProHeart 6. These studies included additional toxicologic and pharmacologic evaluations which suggested the potential allergenic nature of some ProHeart 6 residual solvents. To address the potential for allergens in ProHeart 6, FDAH modified the manufacturing process to eliminate residual solvents. In the following years there was a decline in reported ADEs in international markets. The results of the toxicologic studies coupled with the low frequency of reported ADEs in international markets led to a re-introduction of ProHeart 6

to the US market using a RiskMAP in June 2008, which included tools to mitigate the risks while preserving the benefits of the product. Following the March 24, 2010 VMAC[2], the RiskMAP and associated labeling were revised.

The RiskMAP for ProHeart 6 was updated on August 28, 2013, based on 4.5 years of post-marketing experience collected from 2008 through 2012. The changes to the RiskMAP at that time included:

1. Revised Client Information Sheet (CIS);
2. Removal of the upper age restriction for first dose;
3. Removal of requirement for the signed owner consent form;
4. Relaxed restrictions on product administration and distribution;
5. Increased emphasis on product administration to dogs in good health;
6. Expansion of those qualified to administer ProHeart 6;
7. Updated training materials to reflect changes to the RiskMAP; and
8. A timeline for ongoing RiskMAP assessments.

Since the implementation of the RiskMAP for ProHeart 6, there has been a decrease in reports of death associated with anaphylactic reactions relative to estimated exposure. CVM attributes this decrease to implementation of the tools associated with the RiskMAP aimed at mitigating risk; specifically the web-based RiskMAP training and certification program, client information sheet, and adverse drug experience monitoring. Therefore, the RiskMAP is currently effective in minimizing known risks of ProHeart 6 while preserving its benefits.

ProHeart 12 is being added to the ProHeart 6 RiskMAP because both ProHeart 6 and ProHeart 12 contain the same moxidectin microspheres and the safety profiles for these products are similar; therefore, a similar risk mitigation strategy is appropriate. Implementation of the RiskMAP for ProHeart 12 will provide the same awareness that has been critical for veterinarians to understand the risks associated with administering moxidectin microspheres under ProHeart 6.

ProHeart 12 was approved on July 2, 2019.

ProHeart 6 was approved on June 6, 2001.

Both ProHeart 6 and ProHeart 12 are now marketed under this current RiskMAP.

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1.0 GOAL AND OBJECTIVE

1.1 Goal

The goal of the ProHeart 6 and ProHeart 12 RiskMAP strategy is to reduce the risk of adverse reactions in dogs treated with ProHeart 6, while maintaining the benefit of 6 months of heartworm protection, and to reduce the risk of adverse reactions in dogs treated with ProHeart 12, while maintaining the benefit of 12 months of heartworm protection.

1.2 Objective

The objective of the RiskMAP is to educate veterinary practitioners and pet owners regarding the benefits and risks of ProHeart 6 and ProHeart 12 administration and the safe use of each product in order to mitigate the risks of adverse events. The tools and strategies that have been developed are designed to educate veterinarians and veterinary staff administering the product, and to assist them in educating the pet owners about the benefits and risks of ProHeart 6 and ProHeart 12. The education materials associated with the RiskMAP for ProHeart 6 and ProHeart 12, when properly utilized, should ensure that the veterinarians certified to prescribe and administer the products are educated regarding proper patient selection, the differences and similarities between ProHeart 6 and ProHeart 12, and potential adverse reactions and how to treat them. In turn, the certified veterinarian will be able to educate the pet owner so that adverse reactions, if they occur, are promptly recognized and treated.

2.0 STRATEGY AND TOOLS

2.1 Product Label

The product label is the cornerstone of risk minimization for all FDA-approved products. The approved labels for ProHeart 6 and ProHeart 12 include detailed instructions for use, dosage and administration information, and precautions and warnings associated with the product.

2.2 Comprehensive Educational Program and Communication Plan

2.2.1 Dear Doctor Letter

A “Dear Doctor” letter will be sent by Zoetis that explains revisions to the product labeling and RiskMAP anytime that there are changes to the RiskMAP. This letter will be sent to the veterinarians who have been certified since June 2008, and will review the commitment that these certified veterinarians have made to educate their clients, and the training requirements for non-certified veterinarians, veterinary technicians, and veterinary assistants who may also administer ProHeart 6 and ProHeart 12 under the

supervision of a certified veterinarian.

2.2.2 Web-based Training and Certification*

Prior to purchasing ProHeart 6 or ProHeart 12, each prescribing veterinarian and delegates of the prescribing veterinarian (refer to Section 2.4.1, Administration) must complete a web-based training and certification at Proheartcertification.com that includes:

- Information regarding general safe use guidelines of ProHeart 6 and ProHeart 12;
- Emphasis on administering the drug to healthy dogs;
- Description of the ProHeart 6 and ProHeart 12 label;
- Listing and description of the adverse reactions associated with ProHeart 6 and ProHeart 12;
- Emphasis on the recognition and management of immune reactions, including anaphylaxis;
- Consideration of potential risk factors for adverse reactions including past medical history, pre-existing medical conditions, and current health issues;
- Requirement for enrollment in the ProHeart 6 and ProHeart 12 certification program;
- Use of the CIS as a tool to facilitate veterinary-client discussion;
- Emphasis on the importance of verbal client communication and education prior to administering the drug;
- Emphasis on obtaining the full product lot number and recording this number in the patient record; and
- Requirement to report all suspected adverse events to Zoetis.

* Individuals who have previously taken the web-based training and are certified to order ProHeart 6 may also order ProHeart 12. It is recommended that veterinarians and other staff certified to administer ProHeart 6 and ProHeart 12 annually review the web-based training module.

2.2.3 Client Information Sheet

The CIS will serve as a tool for the veterinarian and their staff to facilitate an active conversation with the client prior to administration of ProHeart 6 or ProHeart 12, in order to emphasize:

- The benefits and risks of the product, including a description of severe allergic reactions.
- That most reactions occur within the first 24 hours after administration of either ProHeart 6 or ProHeart 12.
- The role of the client in observing the dog, especially for severe allergic reactions, and immediately reporting any changes in their pet to the veterinarian.

The client will also be able to take the CIS home with them to refer to should there be any emergency situation, an adverse reaction or question.

Zoetis will ensure that a sufficient number of CISs are supplied when ProHeart 6 or ProHeart 12 is delivered to certified veterinarians. Additionally, an electronic version of the CIS for each product will continue to be available to the veterinarian and owner to view and download from Proheartresources.com.

2.2.4 Informational Websites

There are three web pages dedicated to ProHeart 6 and ProHeart 12: Proheartdvm was developed for veterinarians; Proheart.com for dog owners; and Proheartcertification.com is the web-based training and certification site, which is available for anyone wishing to view the training and become certified. While only licensed veterinarians who complete the certification can purchase product, the web-based training and certification site is available for anyone interested in learning more about ProHeart 6 and ProHeart 12. Anyone planning to administer ProHeart 6 and ProHeart 12 must view the training and certify on the site.

2.3 Toll-Free Telephone Number

A toll-free phone number is available to allow direct contact with the Zoetis Veterinary Medical Information and Product Support (VMIPS) group as a resource to answer questions and report adverse events. The VMIPS toll-free number is included on the CIS, package insert (PI), and product carton.

2.4 Administration and Distribution

2.4.1 Administration

The RiskMAP allows for veterinarians, veterinary technicians, and veterinary assistants, who are not prohibited by law, and who have been certified by completing the training

course and registration, to administer ProHeart 6 and ProHeart 12 under the supervision of a certified veterinarian who has appropriately prescribed and satisfied the conditions of use.

To become certified, veterinarians must complete the training course and understand each commitment involved therewith, particularly the requirement to report adverse events, and ensure that anyone to whom they delegate ProHeart 6 and ProHeart 12 administration has also completed the training and been certified.

A database of certified veterinarian and non-veterinarian registrants who have completed the training will be maintained by Zoetis for reference to ensure that all certified veterinarians and delegates have completed the needed web-based training. Delegation of ProHeart 6 or ProHeart 12 administration to a certified and registered non-veterinarian is allowable provided that the certified veterinarian is present in the hospital at the time of administration in the event that an adverse reaction does take place and the patient needs immediate attention.

2.4.2 Distribution

ProHeart 6 and ProHeart 12 may be shipped from Zoetis authorized distribution agents directly to the clinic that the certified veterinarian designates. As Zoetis agents, these authorized distributors are obligated to comply with the RiskMAP just as Zoetis. Zoetis will ensure that any distributor agent distributing ProHeart 6 and ProHeart 12 will have a protocol in place to verify that all veterinarians ordering ProHeart 6 and ProHeart 12 are certified to use the products in accordance with the RiskMAP before ProHeart 6 or ProHeart 12 is shipped to the clinic. The protocol should also include important processes such as ensuring that a sufficient number of CISs are supplied with ProHeart 6 and ProHeart 12.

2.5 Enhanced Pharmacovigilance Program

Zoetis has a comprehensive pharmacovigilance (PV) program for the collection, evaluation, trending, and reporting of ADEs for all Zoetis marketed products. This is in accordance with worldwide regulatory reporting requirements for PV compliance. Safety information is collected, reviewed, and analyzed on an ongoing basis from multiple sources, including spontaneous reports, reports from health authorities, and reports from published literature. This program enables Zoetis to continually monitor the benefits and risks of administration of ProHeart 6 and

ProHeart 12.

Zoetis maintains a database of ADEs that facilitates the review and reporting of these events to regulatory authorities (refer to Section 2.6, Communication with CVM). All reported ProHeart 6 and ProHeart 12 ADEs are electronically submitted to CVM on a weekly basis. Zoetis provides CVM with a summary and analysis of the adverse event data semiannually (RiskMAP progress report). As part of the enhanced PV program, the RiskMAP progress report focuses on the effect of changes from the original RiskMAP, including the removal of the age restriction on ADEs. This includes, but may not be limited to, continued analyses on the effects and interactions of (1) age, (2) first exposure to ProHeart 6 and ProHeart 12, (3) health status, and (4) any pre-existing medical conditions.

As part of the ADE case evaluation, Zoetis will work with reporting veterinarians and encourage a thorough medical investigation which can include physical exam, laboratory testing, referral to appropriate specialists and necropsy (if indicated). Follow-up information on all ADEs will be obtained whenever possible to determine the event outcome. A Data Collection Guide has been developed for VMIPS to ensure comprehensive description of the event and collection of supporting data including but not limited to signalment, concomitant medical conditions and medications, product lot number, and a detailed description of the event. When provided by the reporter, medical records will be retained with the case.

2.6 Communication with CVM

The following information for ProHeart 6 and ProHeart 12 will be communicated to CVM at the time interval indicated:

- Weekly - adverse drug event reports submitted to CVM;
- Semiannually - Zoetis will present the RiskMAP Progress Report, a summary and analysis of the ADE data for each 6-month period to CVM; and
- Upon request by CVM - manufacturing data will be provided. This includes active pharmaceutical ingredient (API) data; certificate of analysis for each lot or terminal sterilization process; impurities and degradation products associated with each microsphere lot and stability monitoring.

The ProHeart 6 and ProHeart 12 RiskMAP document will be reviewed by Zoetis and CVM at intervals of 1-2 years (not to exceed 2 years), to determine if adjustments to the document are warranted. These regular assessments of the RiskMAP document will ensure that the components of the document are still effective at mitigating the risk of adverse events and that

further adjustments to the document may or may not be needed, consistent with the RiskMAP goals and objectives.

References:

1. January 31, 2005 ProHeart 6 Meeting. Veterinary Medicine Advisory Committee meeting materials and transcript http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm123831.htm
2. March 24, 2010 ProHeart 6 Meeting. Veterinary Medicine Advisory Committee meeting materials and transcript. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/ucm201810.htm