RISK MINIMIZATION ACTION PLAN (RiskMAP) FOR:

PROHEART® 6 (moxidectin) Sustained Release Injectable for Dogs
NADA 141-189

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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) Sustained Release Injectable for 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.

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. Following the March 24, 2010 VMAC[2], the RiskMAP and associated labeling were revised.

This current ProHeart 6 RiskMAP is the latest update to the original RiskMAP, and is based on 4.5 years of post-marketing experience following re-launch of the product. This updated document includes the following changes that are based on an assessment report presented to the Agency on November 5, 2012:

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 consistent with the objectives outlined herein.

The following is the updated ProHeart 6 RiskMAP reflecting revisions outlined in the assessment report.

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1.0 GOAL AND OBJECTIVE

1.1 Goal

The goal of the ProHeart 6 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.

1.2 Objective

The objective of the ProHeart 6 RiskMAP is to educate pet owners and veterinary practitioners regarding the benefits and risks of ProHeart 6 administration and the safe use of the product in order to mitigate the risks of adverse events. The tools and strategies that have been developed are all designed to educate veterinarians and veterinary staff administering the product, and the pet owners acting on behalf of their pets. The ProHeart 6 educational materials, when properly utilized, should ensure that the veterinarians certified to prescribe and administer the product are educated regarding potential adverse events, proper patient selection and the need 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 label includes 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 that 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 that may also administer ProHeart 6 under the supervision of a certified veterinarian.

2.2.2 Web-based Training

Prior to purchasing ProHeart 6, each prescribing veterinarian and delegates of the prescribing veterinarian (refer to Section 2.4.1, Administration) must complete a Web-based training and registration at www.proheart6training.com that includes:

- Information regarding general safe use guidelines of ProHeart 6;
- Emphasis on administering the drug to healthy dogs;
- Description of the ProHeart 6 label;
- Listing and description of the adverse reactions associated with ProHeart 6;
- 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 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 9 digit product lot number and recording this number in the patient record; and
- Requirement to report all suspected adverse events to Zoetis.

2.2.3 Client Information Sheet

Prior to having their dogs treated with ProHeart 6, pet owners will be informed of the benefits and risks by reading the CIS. The CIS will also serve as a tool for the veterinarians and their staff to facilitate an active conversation with the client prior to administration of the product. The CIS emphasizes the role of the client in observing the dog for severe allergic reactions and immediately reporting any changes in their pet to the veterinarian.

Zoetis will ensure that a sufficient number of CISs are supplied when product is delivered to certified veterinarians. Additionally, an electronic version will continue to be available to the veterinarian and owner to view and download from www.proheart6dvm.com and www.proheart6.com respectively.

2.2.4 Informational Websites

There are three ProHeart 6 web pages: www.proheart6dvm.com was developed for veterinarians; www.proheart6.com for dog owners; and www.proheart6training.com is the certification site, which is available for anyone wishing to view and become certified. While only licensed veterinarians who complete the certification can purchase product, the certification site is available for anyone interested in learning more about ProHeart 6. Anyone planning to administer the product 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, 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 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 administration has also completed the training.

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 product 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 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 will have a protocol in place to verify that all veterinarians ordering ProHeart 6 are certified to use the product in accordance with the RiskMAP before product 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.

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 benefit and risk of the administration of ProHeart 6.

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 ADEs are electronically submitted to CVM on a weekly basis. Zoetis provides CVM with a summary and analysis of the adverse event data semiannually. As part of the enhanced PV program, the RiskMAP 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, (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 will be communicated to CVM at the time interval indicated:

- Weekly - adverse drug event reports submitted to CVM;
- Semiannually - Zoetis will present 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 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 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