RISK MINIMIZATION ACTION PLAN (RiskMAP) FOR:

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

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EXECUTIVE SUMMARY

The purpose of this Risk Minimization Action Plan (RiskMAP) is to manage the re-introduction of ProHeart 6 to ensure safe, appropriate use to achieve maximum benefits of heartworm prevention while minimizing risk to dogs.

In 2004, at the request of the U.S. Food and Drug Administration Center for Veterinary Medicine (CVM), Fort Dodge Animal Health (FDAH) instituted a voluntary recall of ProHeart 6. CVM expressed concerns regarding reports of serious adverse events in dogs following use of ProHeart 6. Signals of concern to CVM included anaphylaxis, liver disease, autoimmune hemolytic disease, convulsions and death.

In response to the Agency's concerns, 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. FDAH made changes in the manufacturing process. In the following years there was a decline in the suspected adverse event rate in international markets. The results of the toxicologic studies coupled with the low adverse event frequency in international markets has now led to a restricted return of ProHeart 6 to the US market. In addition, FDAH will put into place a risk minimization plan for ProHeart 6 for the first 12 months of the product's return.

By setting forth a proactive plan of risk minimization activities, the potential for harm associated with use of ProHeart 6 can be reduced and the benefits of better protection extended to individual dogs, as well as to canine populations in heartworm prevalent areas. The objectives of the RiskMAP include:

Veterinarians:

- Provide the reasons for the recall and the new information that has resulted in the restricted return to market.
- Describe the label changes and the reasons for them, including the restriction on concurrent vaccination.
- Describe the requirements for enrollment in the ProHeart 6 prescribing program.

- Describe the need to restrict treatment to healthy dogs between the ages of 6 months and 7 years.
- Describe the need to collect blood sample prior to treatment.
- Understand the need for close monitoring of treated dogs for suspected adverse events and for reporting these promptly to FDAH.
- Provide owners with a client information sheet, answer owners' questions, and obtain a signed informed consent form before each animal is treated.

Dog Owners:

- Provide the risks and benefits of ProHeart 6 through a Client Information Sheet.
- Sign the Informed Consent Form.
- Have open communication with the veterinarian about suspected adverse events.

Fort Dodge Animal Health:

- Implement a comprehensive risk minimization program that communicates new label information to veterinarians.
- Implement education and registration requirements for veterinarians prior to purchase of ProHeart 6.
- Implement monthly electronic submission of all suspected adverse events to CVM as reported to FDAH.
- Identify and interpret possible trends in adverse event reporting and communicate to CVM.

After implementation of the education and registration plan, FDAH will measure awareness of the key messages of the program and knowledge of the conditions of use. Further details of the plan to minimize risk may be found in the remainder of this document. Updates to the RiskMAP will be discussed with CVM on a quarterly basis or as needed, and will include feedback received from veterinarians. Adverse events will be reported to CVM monthly. Risk minimization activities may be modified and alternative methods adopted based on discussions with the CVM.

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1.0 BACKGROUND

In September 2004, at the request of the U.S. Food and Drug Administration Center for Veterinary Medicine (CVM), Fort Dodge Animal Health (FDAH) instituted a voluntary withdrawal of the sustained release heartworm preventive product ProHeart 6 from the U.S. market. CVM expressed concerns about the safety of the product based on the number of voluntarily reported adverse events since product introduction three years earlier.
A Scientific Advisory Panel (Veterinary Medicine Advisory Committee - VMAC) was convened on January 31, 2005, to consider product safety information, and to vote on two questions:

- Based on the presentations and information provided is ProHeart 6 safe for use in dogs? Yes or No.
- If there are remaining safety concerns with ProHeart 6, what additional avenues of research could be explored to mitigate and/or prevent the adverse events?

Of the 15 voting members of the panel, 8 voted "no" and 7 voted "yes"for the demonstrated safety of ProHeart 6 in dogs. The general consensus was that additional research was needed before the product should return to the market.
FDAH has generated considerable additional data in the intervening time as requested by CVM in the intervening time.
ProHeart 6 or similar products are marketed in other heartworm endemic areas, including Europe, Australia and Japan.
Following the VMAC meeting, additional evaluations were conducted on the ProHeart 6 microsphere and vehicle components. These included evaluation of manufacturing changes and the potential impact these changes made on the frequency of suspected adverse event rates over time in major international markets.

1.1 Manufacturing Improvements

ProHeart 6 was approved for sale in the United States in June 2001 and commercialized in the second half of that year. The product under different trade names was introduced in Europe and Japan in 2002 under different trade names, and ProHeart SR-12, a similar product with a higher dose of moxidectin giving longer protection, was introduced in Australia in the last quarter of 2000.

The regulatory agencies in these countries have mandatory adverse event reporting procedures. Initially FDAH received adverse event reports that demonstrated a low but consistent incidence of allergic reactions from all these geographic areas. FDAH undertook extensive investigations to try to determine whether any components of the product were more likely to be allergenic in some dogs. While these investigations failed to identify any individual component as the potential cause of such allergic reactions, FDAH decided in August of 2002, until further research could be performed, to use only batches of moxidectin technical material (MTM) with no detectable residual solvents in the manufacture of the microspheres of this product. From that point forward, MTM with no detectable residual solvents was used exclusively. There was a reduction in the number of reported adverse events in all countries following this change. In the United States, the voluntary adverse event reporting rate fell from a peak of 5.2 per 10,000 doses in 2002, to 2.3 per 10,000 doses the following year. The WHO classification of this adverse event reporting rate in both instances is "Rare". The product was voluntarily withdrawn from the U.S. market at the request of the CVM in September 2004 before these new adverse event data were available for complete analysis.

A second improvement to the raw ingredients was initiated in June 2005 for those ProHeart products in the market when a change in the supplier of the hydroxypropylmethylcellulose (HPMC) used in the vehicle was made. The HPMC supplied by both sources meets both USP and EP compendial standards.

1.2 Immunotoxicology Study

In consultation with CVM and other immunotoxicology experts, a study was conducted in guinea pigs to evaluate the potential immunogenicity of the residual solvent mixture at concentrations many times higher than would occur in the product and the two sources of HPMC when dissolved in the residual solvent mixture. The study design was for intradermal injection of the test substances, scoring of erythema, and scoring and measurement of edema induced by each test substance. The challenge with the residual solvent mixture consistently triggered responses, both erythema and edema. This was evident at the first evaluation timepoint of 30 minutes after injection, and was still evident at the last evaluation timepoint of 48 hours after injection. The severity of reactions increased in a dose dependent manner with increased concentration of the residual solvent solution. There was no apparent impact from the inclusion of HPMC from either source.

A combination of the four residual solvents elicited an anaphylactoid response when administered intradermally to guinea pigs. The findings of this study are relevant to the interpretation of field observations in which a marked decrease in adverse event reports was seen following the manufacturing improvement of using MTM with no detectable residual solvents.

1.3 International Experience with Safety

Major countries where heartworm is endemic and a serious health risk for dogs include Australia, the Mediterranean regions of Europe and Japan. ProHeart 6, its equivalent (GUARDIAN® SR, MOXIDEC® SR) or a similar product (ProHeart® SR-12) are marketed in all of these regions. ProHeart SR-12 is three times the moxidectin dose of ProHeart 6 dose and provides 12 months protection from heartworm infection. These products have established a pattern of safe, effective use in dogs. The raw materials and manufacturing methods for these products are the same as for ProHeart 6. The introduction of the sustained release products occurred at different times and was determined by the regulatory approvals in each market:

- ProHeart SR-12 - Australia in October 2000
- MOXIDEC SR - Japan in September 2001
- GUARDIAN SR - Italy in January 2002, other Concerned Member States (Spain, Greece, Portugal, France) in April/May 2003

The products have achieved substantial usage in all of these countries, with sales of more than 4 million doses in Australia, 3 million doses in Europe, and 2 million doses in Japan. The products are the market leaders in both Australia and Europe with 51% and 42% market shares respectively.

All of these countries have adverse event reporting systems. In each country, the incidence of adverse events showed a decline in 2003 and 2004, regardless of the year or time of first introduction. There was a further decrease in subsequent years, as depicted in the graph below.

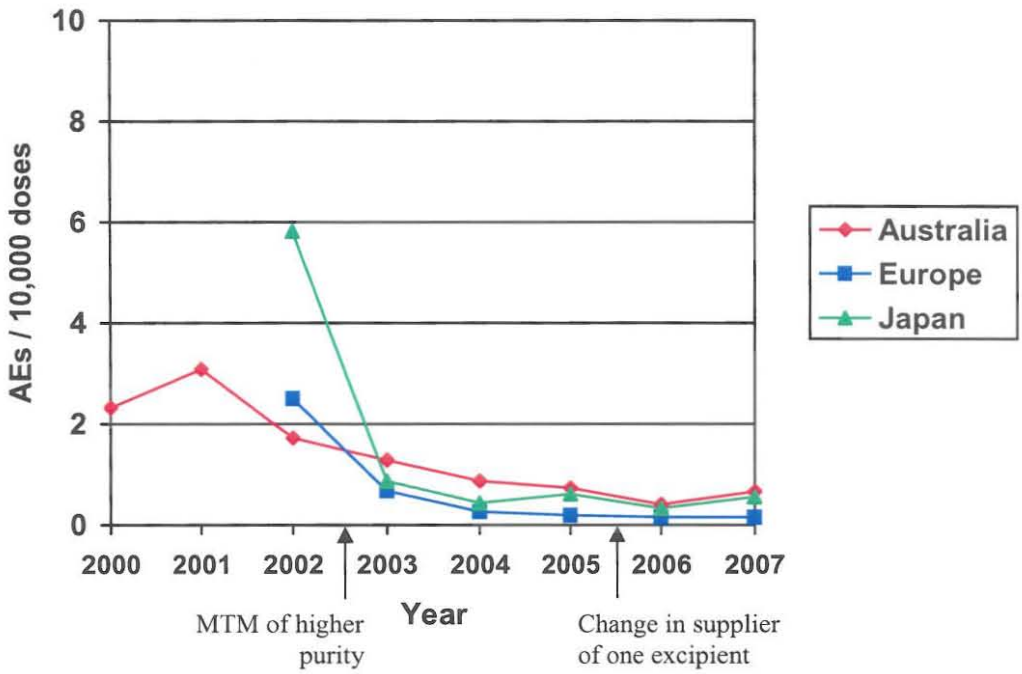

Figure 1-1: Progression of Adverse Events in Different Geographic Regions Over Time

In Australia, the adverse event reporting rate fell from a peak of 3.08 per 10,000 doses sold in 2001 (WHO classification "Rare") to a rate of 0.66 per 10,000 by 2007 (WHO classification "Very rare"). The same pattern was observed in other geographic areas - in Japan from 5.8 per 10,000 in 2002 to 0.55 per 10,000 in 2007, and in Europe from 2.5 per 10,000 in 2002 to 0.15 per 10,000 in 2007. The majority of reported adverse events were allergic in nature. In many cases, the dogs received concurrent vaccinations, making the causality of the reactions unclear. However, it is noted that the decreases in adverse event reporting incidence are coincident with the manufacturing improvement.

2.0 GOALS AND OBJECTIVES

2.1 Goals

The goal of this RiskMAP strategy is:

- Manage the re-introduction of ProHeart 6 to ensure safe, appropriate use, thus maximizing benefits of heartworm protection, while minimizing risk to dogs;

2.2 Objectives

Fort Dodge Animal Health has developed a comprehensive program encompassing:

- A revised product label;
- A comprehensive educational program and communication plan;
- Distribution of the product restricted to veterinarians who have completed training;
- A robust pharmacovigilance system to monitor adverse events; and
- Frequent communication with CVM.

3.0 STRATEGY AND TOOLS

The comprehensive risk minimization program includes all of the following:

3.1 Revised Product Label

The product label is the cornerstone of risk minimization for all FDA-approved products. The newly approved label, provided as Attachment 1, includes additional detailed instructions for use, dosage and administration information, and precautions and warnings associated with the product.

3.2 Comprehensive Educational Program and Communication Plan

3.2.1 Dear Doctor Letter

A "Dear Doctor" letter will be issued by FDAH announcing the return of ProHeart 6 to the U.S. market and outlining FDAH's education and training requirements for veterinarians to prescribe ProHeart 6. This letter will also invite veterinarians to attend the education and training program and provide instructions for participation. (Attachment 2)

3.2.2 Web-based Training

Veterinarian completion of the Web-based training and registration is one of FDAH's conditions of access to ProHeart 6. This module is presented in Attachment 3, and includes:

- New information regarding the safety of ProHeart 6;
- Description of the revised ProHeart 6 label, and Client Information Sheet;
- Listing and description of the serious adverse events of concern to CVM. These are death, anaphylaxis, convulsions, hepatopathy, immune-mediated anemias, immune-mediated thrombocytopenia and weight loss;
- Conditions of ProHeart 6 use, including age eligibility, pre-existing health status, collection of CBC/chemistry panel, RBC and platelet count prior to treatment, and exclusion of concurrent vaccination;
- Requirement for enrollment in the ProHeart 6 prescribing program;
- Requirement to provide the Client Information Sheet to the pet owner, and to answer questions;
- Requirement for a signed Informed Consent form by the pet owner, which will be maintained in the pet's medical record by the veterinarian; and
- Requirement to report all suspected adverse events to FDAH.

3.2.3 Client Information Sheet

In order for pet owners to have their dog treated with ProHeart 6, they will be informed of the benefits and risks by reading the Client Information Sheet (Attachment 4), which includes information about mode of action of sustained-release drugs, safety and efficacy information, precautions, and potential adverse events in a user-friendly 'questions and answers' format. FDAH will ensure a sufficient number of Client Information Sheets will be supplied when product is delivered to registered veterinarians. Additionally, an electronic version will be available for convenient download by veterinarians and pet owners.

3.2.4 Informed Consent

Owners must read and sign the informed consent prior to administration of ProHeart 6. (Attachment 5)

3.2.5 Informational Websites

Separate Websites for veterinarians and pet owners will be available as a communication and education resource. These are http://www.ProHeart6dvm.com and http://www.ProHeart6.com, for veterinarians and owners, respectively. The home page of each of these Websites is provided as Attachment 6.

3.2.6 Toll-Free Telephone Number

A toll-free number will be available for veterinarians. This will allow direct contact with the FDAH Professional Services group both to provide a resource to answer questions and for reporting suspected serious adverse events.

3.3 Restricted Distribution

To become an authorized user of ProHeart 6, veterinarians will have to register with FDAH confirming they have read the new label, the conditions of use, the requirements to provide the owner with the client information sheet and obtain signed informed consent, as well as FDAH's requirement to report adverse events.

3.4 Comprehensive Pharmacovigilance Program

FDAH has a comprehensive validated pharmacovigilance system for the collection, verification, evaluation and reporting of adverse events it receives with the marketed use of its products. This is in accordance with worldwide regulatory reporting requirements for drug safety. New 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. In this proactive manner, FDAH continually monitors the benefit/risk of all of its marketed products.

All adverse events are recorded through the validated PVWorks program, which is managed by the FDAH Professional Services group. All adverse event reports, including ProHeart adverse events, will be submitted to CVM by the FDAH Regulatory Affairs group in accordance with 21 CFR 514.80. Adverse events categorized as "serious, unexpected" will continue to be submitted to CVM as 15-day alert reports. Certain adverse event reports will be subject to special reporting processes, and will be reported as 15 day reports even though they are listed on the label. These adverse events are: anaphylaxis, convulsions, immune mediated hemolytic anemia, immune mediated thrombocytopenia, liver disease and death. Adverse events categorized as "periodic" will be submitted in the annual Drug Experience Report. In addition to these statutory reporting requirements, FDAH will provide completed "Form 1932's" for ProHeart 6 adverse event reports to CVM electronically on CD-ROM on a monthly basis. Evaluation of adverse events reports as a function of ProHeart 6 lot manufacturing parameters may be conducted.

Each individual case will be reviewed as it is received by FDAH. At the end of each quarter, the collected information will be evaluated by the nature and number of adverse events in relation to the number of doses sold. The adverse event data will be evaluated on a monthly basis to identify and interpret trends of adverse events. These reporting rates will be described for the adverse events considered to be serious in nature. These are death, anaphylaxis, convulsions, hepatopathy, auto-immune anemias, immune-mediated thrombocytopenia and weight loss.

As part of the evaluation of adverse events, FDAH will work with the reporting veterinarian to ensure appropriate diagnostic work is conducted in relation to the signs reported. This may include testing by a nationally accessible diagnostic laboratory that uses standardized testing techniques.

3.5 Frequent Communication with CVM

The following will be communicated to the CVM:

- The completed "Form 1932's" will be submitted monthly to CVM by FDAH regulatory affairs via a CD-ROM.
- The CD-ROM will also include pertinent manufacturing parameters:
    - Lot number (finished product (microsphere and vehicle) and API)
    - Certificate of analysis for each lot

  - Certificate of analysis from the terminal sterilization process
  - Impurities/degradation products associated with each microsphere lot
  - Correlate dose to specific lot
  - Lot age at time of product administration.
  - Stability monitoring as requested by CVM
- Trends that may be identified when adverse event data are evaluated.
- Review RiskMAP data and interpretation quarterly or as needed with CVM to determine if adjustments are warranted.
- Review RiskMAP after one year and evaluate and propose label changes and modifications to / termination of the RiskMAP.

Regular evaluation of the RiskMAP will ensure that captured adverse events are reviewed and analyzed in a timely manner and, if appropriate, mitigated by revising the guidelines for veterinarians to follow when using ProHeart 6.

4.0 REFERENCES

Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. U.S. Department of Health and Human Services, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. March 2005.

Guidance for Industry – Development and Use of Risk Minimization Action Plans (RiskMAPs). U.S. Department of Health and Human Services, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. March 2005.

Glickman LT, Glickman NW, Moore GE, Cobb R, Connell SA, Morrison M, Lewis HB. Safety of Moxidectin (ProHeart 6) and Two Oral Heartworm Preventatives in Dogs. *International Journal of Applied Research in Veterinary Medicine*, Vol 3, No 2, 40 – 61, 2005.

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Prevention of Heartworm Infection in Dogs in the Unites States. *International Journal of Applied Research in Veterinary Medicine,* Vol 4, No 4, 339 – 354, 2006.

Genchi C, Rinaldi L, Cascone C, Mortarino M, Cringoli G. Is Heartworm Disease Really Spreading in Europe? *Veterinary Parasitology* 133:(2-3) 137 – 148, 2005.

ATTACHMENT 1 – Product Label

FORT DODGE ANIMAL HEALTH

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30347010

ProHeart® 6

ProHeart® 6

NADA 141-189, Approved by FDA

ProHeart® 6
(moxidectin)

Sustained Release Injectable for Dogs

CAUTION

[illegible]

DESCRIPTION

[illegible]

PHARMACOLOGY

[illegible]

INDICATIONS

[illegible]

DOSAGE AND ADMINISTRATION

[illegible]

DOSAGE CHART

[illegible]

CONTRAINDICATIONS

[illegible]

HUMAN WARNINGS

[illegible]

WARNINGS

[illegible]

PRECAUTIONS

[illegible]

ADVERSE REACTIONS

[illegible]

ANIMAL SAFETY

[illegible]

CONSTITUTION PROCEDURES

[illegible]

STORAGE INFORMATION

[illegible]

HOW SUPPLIED

[illegible]

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

NADA 141-189, Approved by FDA

FORT DODGE®

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. Vial 1 contains 10% moxidectin sterile microspheres and Vial 2 contains a specifically formulated sterile vehicle for constitution with Vial 1. No other diluent should be used. A clear or translucent appearance of the vehicle is normal. Each mL of constituted drug product contains 3.4 mg moxidectin, 3.1% glyceryl tristearate, 2.4% hydroxypropyl methylcellulose, 0.87% 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 milbemycin derivative of nemadectin which is a fermentation product of *Streptomyces cyaneogriseus* subspecies *noncyanogenus*. Moxidectin is a pentacyclic 16-membered lactone macrolide.

Moxidectin has activity resulting in paralysis and death of affected parasites. The stage of the canine heartworm affected at the recommended dose rate of 0.17 mg moxidectin/kg body weight is the tissue larval stage. The larval and adult stages of the canine hookworms, *Ancylostoma caninum* and *Uncinaria stenocephala*, are susceptible.

Following injection with ProHeart 6, peak moxidectin blood levels will be observed approximately 7-14 days after treatment. At the end of the six month dosing interval, residual drug concentrations are negligible. Accordingly, little or no drug accumulation is expected to occur with repeated administrations.

INDICATIONS

ProHeart 6 is indicated for use in dogs six months of age and older for the prevention of heartworm disease caused by *Dirofilaria immitis*.

ProHeart 6 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections.

DOSAGE AND ADMINISTRATION

Frequency of Treatment: ProHeart 6 prevents infection by *D. immitis* for six months. It should be administered within one month of the dog's first exposure to mosquitoes. Follow-up treatments may be given every six months if the dog has continued exposure to mosquitoes and if 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.

ProHeart 6 eliminates the larval and adult stages of *A. caninum* and *U. stenocephala* present at the time of treatment. However, persistent effectiveness has not been established for this indication. Re-infection with *A. caninum* and *U. stenocephala* may occur sooner than 6 months.

Dose: The recommended subcutaneous dose is 0.05 mL of the constituted suspension/kg body weight (0.0227 mL/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 dosage chart may be used as a guide.

DOSAGE CHART

Dog Wt.		Dose Volume	Dog Wt.		Dose Volume
lb	kg	mL/Dog	lb	kg	mL/Dog
11	5	0.25	77	35	1.75
22	10	0.50	88	40	2.00
33	15	0.75	99	45	2.25
44	20	1.00	110	50	2.50
55	25	1.25	121	55	2.75
66	30	1.50	132	60	3.00

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 suspension/kg body weight into an appropriately sized syringe fitted with an 18G or 20G hypodermic needle. Dose promptly 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.

Using aseptic technique, inject the product subcutaneously in the left or right side of the dorsum of the neck cranial to the scapula. No more than 3 mL should be administered in a single site. The location(s) of each injection (left or right side) should be noted so that prior injection sites can be identified and the next injection can be administered on the opposite side.

CONTRAINDICATIONS

ProHeart 6 is contraindicated in animals previously found to be hypersensitive to this drug.

HUMAN WARNINGS

Not for human use. Keep this and all drugs out of the reach of children.

May be slightly irritating to the eyes. May cause slight irritation to the upper respiratory tract if inhaled. May be harmful if swallowed. If contact with the eyes occurs, rinse thoroughly with water for 15 minutes and seek medical attention immediately. If accidental ingestion occurs, contact a Poison Control Center or a physician immediately. The material safety data sheet (MSDS) contains more detailed occupational safety information.

WARNINGS

Do not administer ProHeart 6 within 1 month of vaccinations. ProHeart 6 should be administered with caution in dogs with pre-existing allergic disease, including food allergy, atopy, and flea allergy dermatitis. In some cases, anaphylactic reactions have resulted in liver disease and death. Anaphylactic and anaphylactoid reactions should be treated immediately with the same measures used to treat hypersensitivity reactions to vaccines and other injectable products.

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. Do not administer ProHeart 6 to dogs who are sick, debilitated, underweight or who have a history of weight loss.

PRECAUTIONS

ProHeart 6 should not be used more frequently than every 6 months.

The safety and effectiveness of ProHeart 6 has not been evaluated in dogs less than 6 months of age.

Caution should be used when administering ProHeart 6 to heartworm positive dogs (See **ADVERSE REACTIONS**).

Prior to administration of ProHeart 6, dogs should be tested for existing heartworm infections. Infected dogs should be treated to remove adult heartworms. ProHeart 6 is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, ProHeart 6 is not effective for microfilariae clearance.

ADVERSE REACTIONS

In field studies, the following adverse reactions were observed in dogs treated with ProHeart 6: anaphylaxis, vomiting, diarrhea (with and without blood), listlessness, weight loss, seizures, injection site pruritus, and elevated body temperature. Dogs with clinically significant weight loss (>10%) were more likely to experience a severe adverse reaction.

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 recumbent and required supportive care, than in the dogs with older (6-month-old) infections.

Post-Approval Experience (March 2008): The following adverse reactions are based on voluntary post-approval drug experience reporting. The categories are listed in decreasing order of frequency by body system:

General: Anaphylaxis/loid reactions, depression/lethargy, anorexia, fever, weight loss.

Gastrointestinal: Vomiting (with and without blood), diarrhea (with and without blood), hypersalivation.

Neurological: Convulsions, ataxia, trembling, hind limb paresis

[illegible], peripheral edema, injection site pruritis/swelling, erythema multiforme.

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Gastrointestinal: Vomiting (with and without blood), diarrhea (with and without blood), hypersalivation.

Neurological: Convulsions, ataxia, trembling, hind limb paresis

Dermatological: Urticaria, head/facial edema, injection site pruritis/swelling, erythema multiforme.

Hematological: Immune-mediated hemolytic anemia, leukocytosis, immune-mediated thrombocytopenia

Hepatic: Elevated liver enzymes, hepatopathy, hypoproteinemia, hyperbilirubinemia.

Respiratory: Dyspnea, polypnea, coughing.

Cardiopulmonary signs such as coughing and dyspnea may occur in heartworm-positive dogs treated with ProHeart 6.

In rare situations, death has been reported as an outcome of the adverse events listed above.

To report suspected adverse reactions or to obtain technical assistance, call (800) 533-8536.

ANIMAL SAFETY

General Safety: ProHeart 6 has been administered to a wide variety of healthy dogs six months of age and older, including a wide variety of breeds, pregnant and lactating females, breeding males, and ivermectin-sensitive collies. In clinical studies, two geriatric dogs with a history of weight loss after the initial ProHeart 6 injection died within a month of the second 6 month injection. A third dog who was underweight for its age and breed and who had a history of congenital problems experienced lethargy following the initial injection of ProHeart 6. The dog never recovered and died 3 months later (see **WARNINGS**).

ProHeart 6 administered at 3 times the recommended dose in dogs with patent heartworm infections and up to 5 times the recommended dose in ivermectin-sensitive 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 5 times the recommended dose in 7-8 month old puppies did not cause any systemic adverse effects.

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

In a laboratory safety study, ProHeart 6 was administered at 1, 3 and 5 times the recommended dose to 7-8 month old puppies. Injection sites were clipped to facilitate observation. Slight swelling/edema at the injection site was observed in some dogs from all treated groups. These injection site reactions appeared as quickly as 8 hours post injection and lasted up to 3 weeks. 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 deep subcutaneous thickening were 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 panniculitis with microvacuolation. 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 site reactions were visible grossly 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:

- Microspheres (vial 1)
- Sterile 20 mL syringe for transfer
- Enclosed vent needle (25G)
- Transfer needle (18G or 20G)
- Vehicle (vial 2)

Constitution of the 20 mL vial product.

1. Shake the microsphere vial to break up any aggregates prior to constitution.
2. Using an 18G or 20G needle and sterile syringe withdraw 17.0 mL of the unique vehicle from the vial. **There is more vehicle supplied than the 17.0 mL required.**
3. Insert the enclosed 25G vent needle into the microsphere vial.
4. Slowly transfer the vehicle into the microsphere vial through the stopper using the transfer needle and syringe.
5. Once the vehicle has been added, remove the vent and transfer needles from the microsphere vial. Discard unused vehicle and needles.
6. Shake the microsphere vial vigorously until a thoroughly mixed suspension is produced.
7. Record the time and date of mixing on the microsphere vial.
8. Allow suspension to stand for at least 30 minutes to allow large air bubbles to dissipate.
9. Before <u>every</u> use, gently swirl the mixture to achieve uniform suspension. The microspheres and vehicle will gradually separate on standing.
10. Use a 1 mL or 3 mL syringe and an 18G or 20G needle for dosing. Dose promptly 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.
11. Refrigerate the unused product. The constituted product remains stable for 4 weeks in a refrigerator. Avoid direct sunlight.

STORAGE INFORMATION

Store the unconstituted product at or below 25°C (77°F). Do not expose to light for extended periods of time. After constitution, the product is stable for 4 weeks stored under refrigeration at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

ProHeart 6 is available in the following two package sizes.

1. 5-Pack
   NDC 0856-3670-25 – 20 mL vial product:
   5 - 10% moxidectin sterile microspheres - 598 mg/vial
   5 - Sterile vehicle - 17 mL/vial
2. 10-Pack
   NDC 0856-3670-29 – 20 mL vial product:
   10 - 10% moxidectin sterile microspheres - 598 mg/vial
   10 - Sterile vehicle - 17 mL/vial

For customer service, product information or to obtain a copy of the MSDS, call (800) 533-8536.

U.S. Patent No. 4,916,154 and 6,340,671

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

25700

ATTACHMENT 2 – Dear Doctor Letter

Fort Dodge Animal Health
Division of Wyeth

Tom Lenz, DVM, MS, DACT
Vice President
ProfessionalServices

FORT DODGE

May 2008

Dear Doctor:

Fort Dodge Animal Health today announced the return of ProHeart®6 (moxidectin) to the U.S. veterinary market under a risk minimization and restricted distribution program. As part of the reintroduction of ProHeart 6, Fort Dodge Animal Health will initiate a post-marketing "Risk Minimization Action Plan" (RiskMAP). This program will enable us to educate veterinarians and pet owners and maintain active communication with veterinarians. Fort Dodge Animal Health voluntarily recalled ProHeart 6 in September 2004 to address the U.S. Food and Drug Administration's Center for Veterinary Medicine's (CVM's) safety concerns about the product.

Fort Dodge Animal Health has worked diligently with the CVM to resolve this matter by addressing the Agency's questions regarding the safety of ProHeart 6. Fort Dodge Animal Health followed recommendations made by the 2005 Veterinary Medicine Advisory Committee in conducting studies in the years following the recall to support the reintroduction of the product. Fort Dodge Animal Health feels the extensive safety and review of ProHeart 6 and the substantial scientific data that have been collected and evaluated confirm our confidence in the product and its return to the market.

As part of the RiskMAP program, Fort Dodge Animal Health will require veterinarians who wish to purchase ProHeart 6 to register with the Company and participate in a Web-based training program. In a clinic with multiple practitioners, every veterinarian who plans to use ProHeart 6 must register and be trained. During this training, Company representatives will discuss new label information, and the requirements and restrictions for the use of ProHeart 6.

You may register for this training online at www.vetsymposium.com/proheart6 or contact your Fort Dodge Animal Health representative for assistance. This training will be offered DATE/TIME HERE. The presentation, which is expected to take one hour, will be followed by a question and answer period. For those who are not able to participate in the Web-based training, this presentation and a transcript of the questions and answers will be available beginning DATE HERE on the Web site noted above. Please note Fort Dodge Animal Health will not

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enroll you in this program until you have participated in either the live Web-based or online training.

Thank you to the many veterinarians who offered encouragement and support during the past few years.

Regards,

Tom Lenz, DVM, MS, DACT
Vice President
Professional Services

ProHeart® 6 is generally well tolerated. Do not use in sick, debilitated or underweight animals, animals with a history of weight loss, or within one month of vaccination. Use with caution in dogs with pre-existing allergic disease. A small percentage of dogs showed mild, transient swelling or itching at the injection site. While rare, allergic, digestive, hematological, or neurological reactions may occur. In addition, death has been reported. ProHeart 6 is available only through a restricted distribution program. Only veterinarians enrolled in this program can receive and administer ProHeart 6. In addition, ProHeart 6 must only be administered to clients whose owners have been advised of the risks of ProHeart 6 and sign an Owner Consent Form. To obtain additional information including a copy of the product labeling, visit the website at www.proheart6dvm.com or call 1-800-533-8536.

ATTACHMENT 3 – Web-based Training Materials

ProHeart® 6
(moxidectin)

® Registered trademark

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Fort Dodge Animal Health

ProHeart® 6
(moxidectin)

Web-based Training for Veterinarians

- Introductory Remarks
- Return of ProHeart® 6 to Market
- Label Changes
- Post-Marketing Requirements
- Closing Remarks

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Fort Dodge Animal Health

ProHeart® 6
(moxidectin)

Purpose of Educational Slides for ProHeart 6 (moxidectin) Sustained Release Injection for Dogs

- By reviewing this educational material for ProHeart 6, veterinarians should be able to understand:
  - Important safety information
  - The restricted conditions of use
  - The requirements for reporting adverse events

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Fort Dodge Animal Health

ProHeart®6
(moxidectin)

Opening Remarks

- Welcome remarks and introductions
- Training objectives/agenda
- Brief product history
- Thank you for your support

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ProHeart® 6
(moxidectin)

Return of ProHeart 6 to U.S. Market

- Studies and evaluations conducted since product recall
- Improvements in Manufacturing
- International experience with moxidectin SR products in dogs

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ProHeart® 6
(moxidectin)

Studies and Evaluations Conducted Since 2005 VMAC

1. Moxidectin Toxicology and Mechanism of Action
   - Pharmacokinetic analysis of moxidectin in rats' and dogs' serum:
     - Toxicology studies confirmed the mammalian safety profile of moxidectin
     - No adverse effects in mice or rats receiving >5mg/kg/day for two years
     - No adverse effects in dogs receiving 1mg/kg/day for one year
     - Cumulative exposure (AUC) in dogs in this study at the NOAEL was 454-fold higher than after two doses of ProHeart 6, six months apart
     - Cumulative exposure in rats in this study was 860-fold higher than after four doses of ProHeart 6 given six months apart

ProHeart® 6
(moxidectin)

Studies and Evaluations Conducted Since 2005 VMAC

- Previous metabolism studies in various mammalian species identified the following characteristics for moxidectin:
  - No major significant metabolites
  - No drug – drug interaction potential

ProHeart®6
(moxidectin)

Studies and Evaluations Conducted Since 2005 VMAC

2. In-Vitro Binding Studies

- Both moxidectin and moxidectin-containing microspheres were evaluated in a receptor binding selectivity screen.
- Replicated assays of 63 different receptors and enzymes were conducted:
  - 29 distinct neurotransmitter-related functions
  - 2 steroids
  - 6 ion channels
  - Nitric oxide (second messenger)
  - 3 prostaglandins
  - 4 growth factors/hormones
  - 13 brain/gut peptides
  - 5 enzymes
- These assays did not identify any significant potential for unexpected target toxicity, either for moxidectin or moxidectin-containing microspheres.

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ProHeart® 6
(moxidectin)

Studies and Evaluations Conducted Since 2005 VMAC

3. Evaluation of Formulation and Manufacturing Processes

- Two improvements have been made since the launch of ProHeart 6:
  - In August 2002, a decision was made to use moxidectin technical material (MTM) with residual solvents below any detectable level.
  - In July 2005, the supplier of one of the excipients was changed.
- Global production of moxidectin sustained release injection for dogs occurs at our manufacturing site in Fort Dodge, Iowa. The raw materials and manufacturing processes are the same for all markets for ProHeart 6, GUARDIAN SR, and MOXIDEC SR 6. The fill volume of microspheres is higher for ProHeart SR 12. All other processes for this product are the same.

ProHeart® 6
(moxidectin)

Studies and Evaluations Conducted Since 2005 VMAC

4. Immunotoxicology Studies

- In consultation with FDA and immunotoxicology experts, studies were conducted in guinea pigs to evaluate the potential immunotoxicity of MTM residual solvent mixtures.
- The residual solvent mixtures were shown to induce dermal reactions as measured by redness and edema when given intradermally in guinea pigs.
- The severity of reactions increased in a dose-dependent manner with increased concentration of the residual solvent solution.

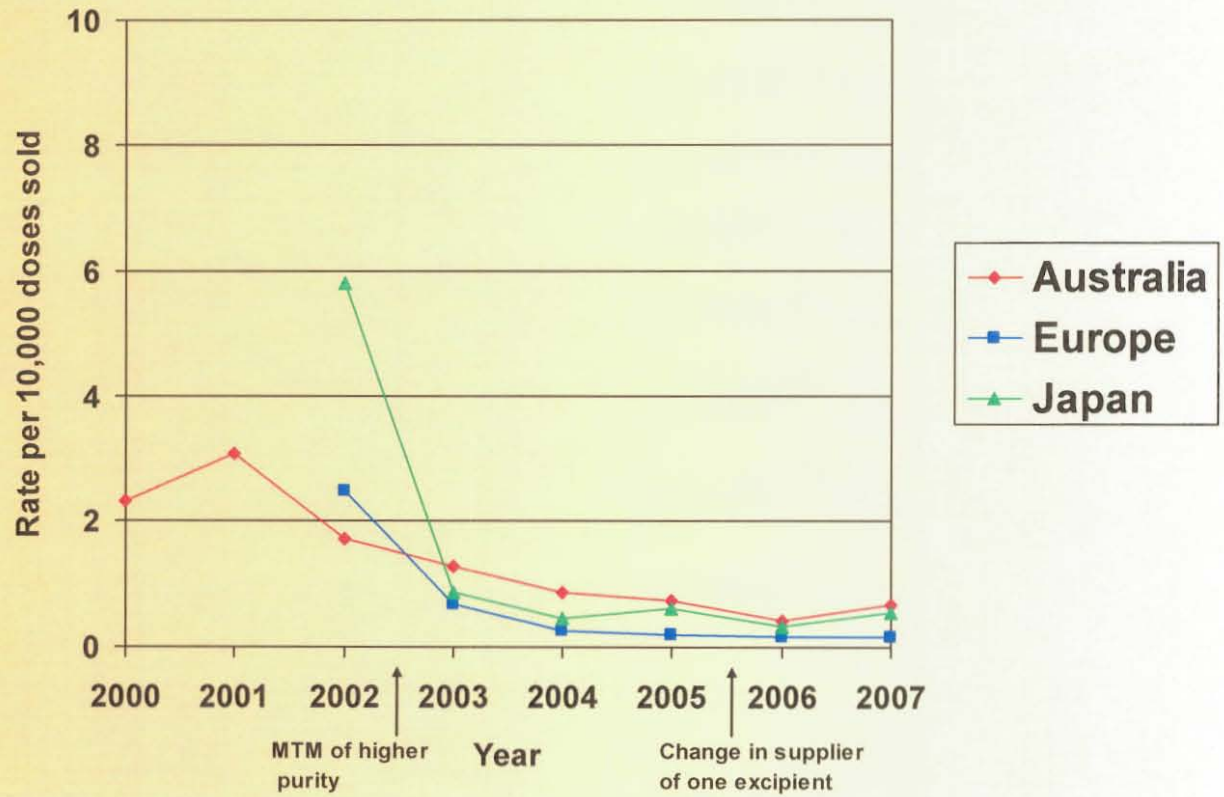
ProHeart® 6
(moxidectin)

International Experience AER Rates by Year by Geographic Region

5. International experience
   - ProHeart 6 or similar products were commercially available in multiple geographies starting in 2000.
   - Significant market share in:
     - Australia: 51%
     - Europe (Italy): 42%
   - FDAH collects and reports adverse events worldwide.

ProHeart® 6
(moxidectin)

International Experience AER Rates by Year by Geographic Region



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ProHeart® 6
(moxidectin)

Label Changes

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ProHeart® 6
(moxidectin)

Label Changes

- Warnings
  - Do not administer ProHeart 6 within one month of vaccinations.

ProHeart®6
(moxidectin)

Label Changes

- Warnings
  - Administer with caution to dogs with pre-existing allergic disease:
    - Food allergy
    - Atopy
    - Flea allergy dermatitis
  - Do not administer to dogs that are sick, debilitated, underweight or have a history of weight loss.

ProHeart®6
(moxidectin)

Label Changes

- Adverse Reactions
  - Field Studies – adverse reactions observed were anaphylaxis, vomiting, diarrhea (with and without blood), listlessness, weight loss, seizures, injection site pruritus and elevated temperature. Dogs with clinically significant weight loss (>10%) were more likely to experience a severe adverse reaction.
  - In a laboratory 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 the 4-month-old heartworm infections, including one dog that was recumbent and required supportive care, than in the dogs with older (6-month-old) infections. (Not noted on label, untreated control dogs showed a similar incidence of the same signs.)

ProHeart® 6
(moxidectin)

Label Changes

- Post Approval Experience
  - General
    - Anaphylaxis/toid, depression/lethargy, anorexia, fever, weight loss
  - Gastrointestinal
    - Vomiting and/or diarrhea with or without blood, hypersalivation
  - Neurological
    - Convulsions, ataxia, trembling, hind limb paresis
  - Dermatological
    - Urticaria, head/facial edema, injection site pruritis/swelling, erythema multiforme

ProHeart® 6
(moxidectin)

Label Changes

- Post Approval Experience (cont)
  - Hematological – Immune-mediated hemolytic anemia, leukocytosis, immune-mediated thrombocytopenia
  - Hepatic – Elevated liver enzymes, hepatopathy, hypoproteinemia, hyperbilirubinemia
  - Respiratory – Dyspnea, polypnea, coughing. Cardiopulmonary signs, such as coughing and dyspnea, may occur in heartworm positive dogs treated with ProHeart 6

In rare situations, death has been reported as an outcome of the adverse events listed above.

ProHeart® 6
(moxidectin)

Post Marketing Commitments

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ProHeart® 6
(moxidectin)

ProHeart 6 Post-Marketing Commitments

- Risk Minimization Action Plan (RiskMAP)
  - A proactive plan of risk minimization activities has been developed and includes:
    - An educational program for veterinarians covering the risks and benefits of ProHeart 6 as well as information for owners.
    - Veterinarians wishing to use ProHeart 6 must complete the training program and register as ProHeart 6 users.

ProHeart® 6
(moxidectin)

ProHeart 6 RiskMAP

Veterinarians' Actions

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ProHeart® 6
(moxidectin)

ProHeart 6 RiskMAP

- Only veterinarians trained on the RiskMAP may administer ProHeart 6.
- Veterinarians using ProHeart 6 must commit to report adverse events to FDAH.

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ProHeart® 6
(moxidectin)

ProHeart 6 RiskMAP

- ProHeart 6 is to be used in dogs aged 6 months to 7 years.
  - The lower age limit is mandated by the label.

ProHeart® 6
(moxidectin)

ProHeart 6 RiskMAP

- ProHeart 6 is not to be used within 30 days of vaccination.

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ProHeart® 6
(moxidectin)

ProHeart 6 RiskMAP

- Prior to administration
  - ➢ Routine collection of history and physical exam findings to confirm patient is appropriate candidate for ProHeart 6.
  - ➢ Negative heartworm test.
  - ➢ Collect CBC/chemistry to evaluate baseline liver function, RBC and platelet count.
  - ➢ Review ProHeart 6 use with client:
    - Provide Client Information Sheet
    - Obtain signed Consent Form
    - Retain signed Consent Form
  - ➢ Record lot number on medical record

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ProHeart® 6
(moxidectin)

ProHeart 6 RiskMAP

- Management of anaphylaxis and allergic reactions
  - ➢ Systemic anaphylaxis
    - Based on clinical signs may become an emergency condition requiring life support, including:
      - Maintenance of airway
      - Prevention of circulatory collapse
        - » fluids, epinephrine, steroids, others
      - Management of GI signs
  - ➢ Anaphylactoid reactions (Example urticaria)
    - Generally not life threatening
    - Generally requires antihistamines and/or steroids
    - Need to prevent systemic involvement
  - ➢ Attending veterinarian is best qualified to select appropriate treatment for the patient.

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ProHeart® 6
(moxidectin)

ProHeart 6 Post-Marketing Requirements

- Risk Minimization Action Plan (RiskMAP)
  - FDAH will report adverse events to CVM on a monthly basis, in addition to the statutory reporting requirements.
  - The RiskMAP will be reviewed and adjusted based on field experience and feedback from veterinarians.
  - After one year, the RiskMAP will be revised, any appropriate label changes will be implemented, and the RiskMAP modified or terminated.

ProHeart® 6
(moxidectin)

ProHeart 6 Communication and Education Plan

- For Veterinarians
  - A communication tool kit will be provided to veterinarians purchasing ProHeart 6:
    - Product Label
    - Letter to the veterinary community
    - Online training program
    - ProHeart6dvm.com Web site
    - 800 number connecting to FDAH Professional Services

ProHeart® 6
(moxidectin)

ProHeart 6 Communication and Education Plan

- Client education materials provided to clinics for distribution to animal owners:
  - Pet Owner Letter
  - Client Information Sheet
  - ProHeart6.com Web site

ProHeart®6
(moxidectin)

Client Information/Informed Consent Process

Discuss Client Information Sheet and describe Informed Consent Form

Sign Informed Consent Form

Maintain Consent Form in Patient's Medical Record

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Fort Dodge Animal Health

ProHeart®6
(moxidectin)

Veterinary Support for Sustained Release Heartworm Control

- 11% of veterinarians reporting increased sales of heartworm preventives also reported they were seeing more cases of heartworm in their area.
- The likelihood of veterinarians using a 12-month heartworm preventive to protect dogs in their care has similarly increased.

	2004	2005	2006
Very likely	**29%**	**36%**	**42%**
Somewhat likely	**23%**	**22%**	**24%**
Not very likely	**11%**	**8%**	**7%**
Not at all likely	**4%**	**3%**	**2%**
Not sure – need more information	**33%**	**30%**	**25%**

Brakke Consulting, The U.S. Flea Control and Heartworm Markets 2006

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Fort Dodge Animal Health

ProHeart® 6
(moxidectin)

Closing Remarks

- Timeline for introduction
- Reiterate requirements for product utilization
- For more information (contacts)
- Thank you for participating

ATTACHMENT 4 – Client Information Sheet

Client Information about ProHeart® 6 (moxidectin)

ProHeart 6 (pronounced "Pro-hart" "six")
Generic name: moxidectin ("mox-ee-deck-tin")

This summary contains important information about ProHeart 6. You should read this information before your veterinarian administers ProHeart 6 to your dog and review it each time your dog is retreated. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about ProHeart 6.

What is ProHeart 6 and why has my veterinarian prescribed ProHeart 6?

ProHeart 6 is an injectable parasiticide that is used in dogs six months of age and older to prevent heartworm disease *(Dirofilaria immitis)* continuously for six months and to treat common hookworm infections *(Ancylostoma caninum* and *Uncinaria stenocephala)*.

What should I discuss with my veterinarian before ProHeart 6 is prescribed?

Your veterinarian is your best resource for recommending appropriate medications for your dog. It is important to discuss your dog's health history with your veterinarian so he/she can decide if ProHeart 6 is right for your dog.

Which dogs should not be treated with ProHeart 6?

ProHeart 6 should not be used in sick, debilitated or underweight animals. ProHeart 6 should be given with caution in dogs with pre-existing allergic disease, including previous vaccine reactions, food allergy, atopy, and flea allergy dermatitis. Dogs should be tested for heartworm disease prior to being treated with ProHeart 6. If your dog tests positive for adult heartworms, your veterinarian should treat the infection with an appropriate medication before administering ProHeart 6.

What possible side effects of ProHeart 6 should I look for in my dog?

- Severe allergic reactions (anaphylaxis): facial swelling, itching, difficulty breathing, collapse
- Lethargy (sluggishness), not eating or losing interest in food, any change in activity level
- Seizures
- Vomiting and/or diarrhea (with and without blood)
- Weight loss
- Pale gums, increased thirst or urination, weakness, bleeding, bruising

- **If you notice any of these side effects or have any concerns about your dog, please contact your veterinarian as soon as possible.**

Can ProHeart 6 be given with other medicines?

In well-controlled clinical studies, ProHeart 6 was used safely in dogs receiving other veterinary products such as antihelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics, and flea control products. ProHeart 6 should not be given within one month of your dog being vaccinated. Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to use with ProHeart 6.

How long will ProHeart 6 remain in the body?

Several studies have shown that by the end of the six-month treatment period, the amount of ProHeart 6 remaining in the body is too small to measure. An additional study demonstrated that after four consecutive treatments there was no accumulation of ProHeart 6 over time.

What else should I know about ProHeart 6?

This sheet provides a summary of information about ProHeart 6. If you have any questions or concerns about ProHeart 6, talk to your veterinarian.

Read the package insert for more information.

To obtain additional information visit the website at www.proheart6.com, or call 1-877-6PROHEART (1-877-677-6432).

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

01028 Revised April 2008 3670G

Client Information about ProHeart® 6 (moxidectin)

ProHeart 6 (pronounced "Pro-hart" "six")
Generic name: moxidectin ("mox-ee-deck-tin")

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What should I discuss with my veterinarian before ProHeart 6 is prescribed?

Your veterinarian is your best resource for recommending appropriate medications for your dog. It is important to discuss your dog's health history with your veterinarian so he/she can decide if ProHeart 6 is right for your dog.

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- Lethargy (sluggishness), not eating or losing interest in food, any change in activity level
- Seizures
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- Weight loss
- Pale gums, increased thirst or urination, weakness, bleeding, bruising

- **If you notice any of these side effects or have any concerns about your dog, please contact your veterinarian as soon as possible.**

Can ProHeart 6 be given with other medicines?

In well-controlled clinical studies, ProHeart 6 was used safely in dogs receiving other veterinary products such as anthelmintics, antiparasitics, antibiotics, analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics, and flea control products. Proheart 6 should not be given within one month of your dog being vaccinated. Tell your veterinarian about all medicines you have given your dog in the past, and any medicines that you are planning to use with ProHeart 6.

How long will ProHeart 6 remain in the body?

Several studies have shown that by the end of the six-month treatment period, the amount of ProHeart 6 remaining in the body is too small to measure. An additional study demonstrated that after four consecutive treatments there was no accumulation of ProHeart 6 over time.

What else should I know about ProHeart 6?

- Pale gums, increased thirst or urination, weakness, bleeding, bruising

- **If you notice any of these side effects or have any concerns about your dog, please contact your veterinarian as soon as possible.**

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How long will ProHeart 6 remain in the body?

Several studies have shown that by the end of the six-month treatment period, the amount of ProHeart 6 remaining in the body is too small to measure. An additional study demonstrated that after four consecutive treatments there was no accumulation of ProHeart 6 over time.

What else should I know about ProHeart 6?

This sheet provides a summary of information about ProHeart 6. If you have any questions or concerns about ProHeart 6, talk to your veterinarian.

Read the package insert for more information.

To obtain additional information visit the website at www.proheart6.com, or call 1-877-6PROHEART (1-877-677-6432).

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

01028 Revised April 2008 3670G

ATTACHMENT 5 – Client Informed Consent

PROHEART® 6 OWNER CONSENT FORM

Having read the ProHeart 6 Client Information Sheet, I consent to allow my dog to be administered ProHeart 6. I understand that ProHeart 6 is a medicine used to prevent heartworm disease in dogs continuously for six months and to treat common hookworm infections in dogs. My veterinarian has told me about choices for preventing heartworm disease and treating hookworm infections in my dog. I am aware of the possible side effects of ProHeart 6 in dogs. These have been explained to me. These side effects include severe allergic reactions, change in activity level, seizures, vomiting, diarrhea, weight loss, bleeding, and bruising. I agree to report any changes in my dog's health status to my veterinarian and to seek appropriate medical attention, if necessary, from my attending veterinarian. I understand this product is subject to restricted distribution and may only be administered by a veterinarian who is trained on the appropriate use of the product.

I, _____ , have read and understand the information describing this product and all my questions have been answered to my satisfaction by my veterinarian. I am the owner of the dog _____ (print dog's name or identification number) and now authorize my veterinarian to begin treating my dog with ProHeart 6.

Signed: _____ Date:
Owner or Designated Representative

Attending Veterinarian: _____ Date:

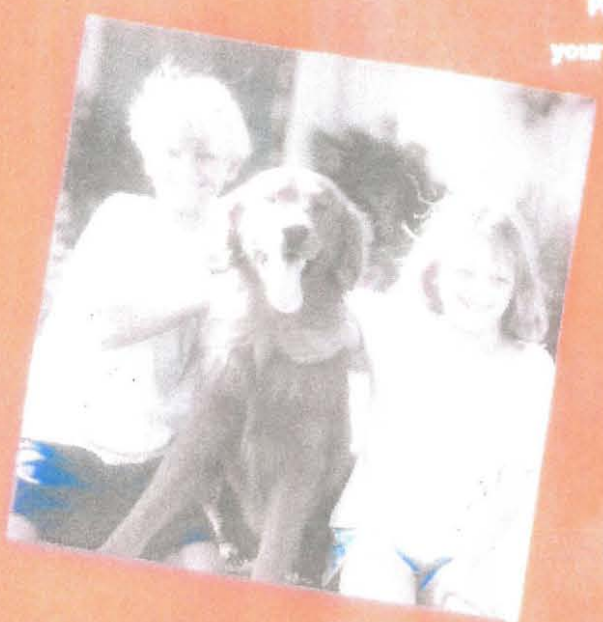
ATTACHMENT 6 – Website Home Pages

ProHeart® 6
(moxidectin)

Information for dog owners

About ProHeart® 6 | Heartworm Disease | FAQs | Ask the Vet | Get In Touch With Us | News | Product Label | Email Reminder

Six months of heartworm protection in one dose.



ProHeart® 6 is [illegible] administered by your veterinarian [illegible] to remember (or forget) [illegible] from [illegible].

[illegible] your veterinarian [illegible] source for information [illegible] ProHeart® 6 and heartworm [illegible].

Proud sponsor of:

ProHeart6
(moxidectin)

Home | About ProHeart6 | Heartworm Disease | FAQs | News | Product Information

Heartworm protection Controlled by Veterinarians

ProHeart6 now comes with an extra dose of confidence.

Here's some content for the first paragraph, which would go right in here. The headlines could be in the same font as the logo. » full story

Provides six months of protection in one dose.

This is content for the second paragraph. Content for the second paragraph goes here.

» full story

Heartworm protection that **you** control.

Content for the third paragraph goes here.

» full story