

US EPA ARCHIVE DOCUMENT



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: September 16, 2005

MEMORANDUM

Subject: EPA File Symbol: 80490-E PROMERIS SPOT-ON FOR DOGS
DP Barcode: D319379
Decision No.: 351841
PC Codes: 106201 (Amitraz); 281250 (Metaflumizone)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
9/16/2005
→ CK
9/23/05

To: Ann Hanger/John Hebert RM 07
Insecticide Branch
Registration Division (7505C)

Applicant: FORT DODGE ANIMAL HEALTH

FORMULATION DECLARATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
Metaflumizone (CAS #139968-49-3).....	14.34%
Amitraz (CAS #33089-61-1).....	14.34%
<u>Other Ingredients:</u>	71.32%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

"This bean sheet is being generated to go with Fort Dodge's response to your 5/27/05 animal safety data DER (DP#311482). Fort Dodge's response was sent via email on 7/6/05."

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BACKGROUND: The registrant has responded to a previous TRB review (dated 27 May 2005) of two companion animal (adult dog and puppy) studies conducted on this formulation.

COMMENTS AND RECOMMENDATIONS:

1. The major area of TRB's concerns regarding this product are the indications - largely 24-hour postexposure clinical chemistry values for glucose and BUN - that one of the actives - amitraz - is absorbed in physiologically significant amounts.

This reviewer agrees that comparisons to historical control data from beagles tested at MPI are more appropriate than values from UMn. However, an examination of the MPI historical control data does not change the conclusion that there were effects (both in the adult dog and puppy study) involving glucose and BUN, indicating that sufficient amounts of amitraz were being absorbed to affect hypothalamic function. As noted in the OPPTS 870.7200 Guidelines: "The targeted adequate margin of safety is 5X. Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)..."

TABLE 1. Comparison of MPI & UMn Glucose values (mg/dL)				
Parameter	MPI Mean	MPI Mean \pm 2 S.D.	MPI Individual Animal Range	UMn Reference
Males 0-3 months	102.4	85-120	82-126	80-120
Females 0-3 months	97.7	76-119	73-124	80-120
Males 4-6 months	96.0	79-113	78-115	80-120
Females 4-6 months	94.2	73-115	55-111	80-120

TABLE 2. Comparison of MPI & UMn BUN values (mg/dL)				
Parameter	MPI Mean	MPI Mean \pm 2 S.D.	MPI Individual Animal Range	UMn Reference
Males 0-3 months	9.6	4-15	4-16	7-24
Females 0-3 months	10.0	6-16	6-17	7-24
Males 4-6 months	11.9	7-17	7-19	7-24
Females 4-6 months	13.7	8-19	6-21	7-24

2. TRB is still concerned about the occurrence of death of a 3X female (#122) in the puppy study, and the possibility that this death may have been related to administration of and exposure to the test material.
3. As part of the registrant's response to the original TRB review, the registrant has cited (and summarized) four additional studies conducted on dogs with ProMeris

Spot-On. Complete copies of these additional studies should be submitted to the Agency.

4. TRB recommends that this registrant's response, along with the copies of the four additional studies, be referred to HED in order to conduct a primary review and risk assessment for the proposed use(s) of the ProMeris Spot-On formulation. Hopefully, after review of the four additional studies the significance of the glucose and BUN elevations seen in the original companion animal (adult dog & puppy) studies will be addressed as part of the risk assessment process.
5. Since additional time will be required to review the four studies, the PRIA due date will have to be renegotiated.
6. If the product is registered, TRB strongly recommends that it be available only through veterinarians. This labeling restriction can be taken into consideration as part of the HED risk assessment process.

Reference: EPA letter dated 27 May 2005

The reference letter provides comments on two safety studies in dogs (MRID 46401003 and 46401004) for ProMeris Spot-on For Dogs (EPA File Symbol 80490). While Fort Dodge Animal Health (FDAH) appreciates the prompt and thorough review of these studies by EPA, we do not agree with the conclusion that the studies do not demonstrate an adequate margin of safety for ProMeris and, thus, do not support registration.

The purpose of this communication is to respond to the points raised by the EPA on these studies. In addition to some general comments, each point will be individually addressed. To support this response, data from studies that have been conducted to support the registration of ProMeris in other countries and not formally submitted to EPA will be cited. Summaries of each cited report are included with this response (Appendix A). Copies of the full reports or pdf files of the text are available. These studies are as follows:

Study	Title	Brief Description
0817-C-US-12-04	Safety evaluation study of repeated treatments with a topically applied spot-on formulation of R-28153 and amitraz in dogs.	Placebo, 1, 3, 5X dosing; 7 doses at 2 week intervals. Dogs 10 weeks of age at start. Physical, neurological, clinical exams. Full clinical chemistry and hematology.
0817-C-US-14-04	Safety evaluation study of oral exposure from auto-or allogrooming R-28153/amitraz spot-on formulation in dogs.	Oral dose; 10% of topical dose vs saline control. 6 month old dogs. Same observations as above.
0817-C-SA-02-04	Evaluation of the toxicity in Chihuahua breed dogs of an insecticidal spot-on for dogs containing R-28153, 150 mg and amitraz, 150 mg/mL.	Puppies/dogs 0.55 to 2 kg dosed with 0.67 mL at 0 and 14 days. Physical, clinical exams. Clinical chemistry and hematology.
0817-C-FR-06-04	Pharmacokinetics of R-28153 and Amitraz after a single topical application to dogs at 20 mg/kg of R-28153 and Amitraz.	6 Beagles dosed at 0.13 mL/kg. Blood samples at 5, 10 hr and periodically through 56 days. Plasma assayed for amitraz and metaflumizone.

I. General Comments on the Review

- A) Non-contemporaneous clinical pathology values (from the U. of Minnesota Diagnostic Lab) are used as reference values in the review. Clinical pathology results from contemporaneous controls are the most valid measurement for comparison and contemporary controls were included in every study. Comparisons

made in the review to reference ranges from UMn may be misleading because a) UMn reference ranges are generated from dogs of various breeds and ages, dogs that are not representative of the study population (young, line-bred/inbred Beagles), and b) laboratory methods differ so that a value generated in one lab is not necessarily comparable to a value generated in another lab. If clinical pathology data are to be compared to reference ranges rather than contemporaneous controls, then references from historical controls generated at MPI, derived from Covance Beagles of similar age and gender, should be used. For convenience, copies of MPI historical control data for Beagles 0-3 and 4-6 months of age are included in Appendix B.

B) The review includes conclusions based on assumptions that this topically applied product will behave similarly and cause toxicities with an existing amitraz product, Mitaban®, or as noted following oral ingestion of amitraz. A number of topically applied products would cause toxicity if ingested yet are used safely because methods of use limit the risk of oral exposure (low volume, small and difficult to access application area). Such is the case with ProMeris, which is applied as a low volume spot-on to a small area between the shoulder blades. By contrast, Mitaban is applied at a high volume to cover the entire surface of the animal. This increases the likelihood of oral exposure. Because of the differences in formulation and administration, extrapolation of Mitaban toxicity to ProMeris is not appropriate.

II. Direct comments on items listed in the COMMENTS AND RECOMMENDATIONS follow. For ease of review, each point in the letter is presented in **bold**, followed by the FDAH response.

1. While the conduct and reporting of the companion animal (adult dog) safety study (OPPTS 870.7200) in MRID 46401003 (OPPTS 870.7200) were adequate, the study does not demonstrate an adequate margin of safety (5X) associated with the proposed use of this formulation, and so does not support registration.

FDAH does not concur with the statement “the study does not demonstrate an adequate margin of safety (5X) associated with the proposed use of this formulation, and so does not support registration.” Section (g) (3) of OPPTS 870.7200 states “The targeted adequate margin of safety is 5X. Consideration will be given to products with less than a 5X margin of safety, depending on the severity of clinical signs of toxicity (e.g. transient, non-life-threatening signs)”. As occurs in many studies of this type, there were statistically significant differences between treated and control groups in some of the parameters measured. However, the researchers conducting the study evaluated these findings and concluded that they were not physiologically relevant and/or were mild and transient in nature, therefore not biologically significant and clearly non-life-threatening. This appears to fit the definition provided in the guideline.

i. A depressed righting reflex was seen in 4/12 of the 5X dogs. In two of

these dogs it was observed on Days 1, 2, 8 and 22, indicating the possibility of a permanent effect.

The test for righting reflex can be influenced by conscious behavior. Since the body placement for the test is a submissive position for dogs, it is not uncommon for laboratory beagles to voluntarily remain in the position. There were occasional observations of dogs with depressed righting reflex noted in the puppy study (MRID 46401004), occurring in all treatment groups. These were "considered to be due to a behavioral attitude rather than a true neurological response". A depressed righting reflex in the absence of any other neurological findings is not considered significant because of the nature of the exam.

Study 0817-C-US-12-04 was a repeated treatment study in dogs conducted by the same laboratory as were the studies provided in MRID 46401003 and 46401004. The conduct and data recorded for this study was similar to the cited studies except that the animals were treated a total of seven times at two-week intervals. The dogs were 10 weeks of age at the start of the study. Treatment groups were 1X, 3X 5X and placebo applied at a volume of 5X as in the previous studies. No pattern of depressed righting reflex was observed in dogs in this study even under the exaggerated treatment regimen. Depressed righting reflex was only observed in one pup that was euthanized on Day 3 for reasons considered unrelated to treatment. This pup showed clinical signs of illness prior to treatment.

- ii. All dogs (including those at OX) were very quiet and inactive ("little activity or barking compared to the previous day, even during repeated entries by the technical staff) on the afternoon of Day 1 (applications of test material or placebo were made during the morning). While the report states that this could be a result of increased handling which had occurred earlier (during application of the test substance or placebo), Amitraz can cause sedation. Although dogs in the placebo control group also showed the same or a similar effect, one or more of the inerts in this formulation (may) have pharmacological activity, and these controls were being exposed to essentially a 7X dosage of the formulation without the actives.**

This observation appears to refer to the DEET in the formulation. Although DEET has pharmacological activity, the literature indicates that clinical signs of suspected acute DEET toxicity in dogs includes vomiting, tremors, excitation, ataxia and seizures. Dogs fed 300mg/kg/day for 13 weeks displayed tremors, hyperactivity and occasionally vomiting. The reduced activity noted in all dogs is not consistent with reported effects of DEET toxicity. Thus, there appears to be no justification to discount the quiet behavior noted in controls. In addition, there was no apparent dose relationship to either the active ingredients or excipients. Also, this finding was not corroborated in the puppy study (MRID 46401004) or in any of the other target animal safety studies or the laboratory

efficacy trials conducted with ProMeris.

By contrast, sedative effects were noted in Study 0817-C-US-14-04, conducted to determine the safety of oral exposure to ProMeris that might occur with auto- or allogrooming in dogs following treatment. This study was conducted by the same laboratory as were the studies provided in MRID 46401003 and 46401004. Eight dogs received an oral dose of ProMeris equivalent to 10% of the recommend topical dose (approximately 3 mg each of R-28153 and amitraz/kg body weight). A similar group of control dogs received saline orally at the same dose volume. Clinical signs including decreased activity, ataxia and reduced body temperature were noted in approximately half of the treated dogs, starting within one hour of treatment. Signs resolved spontaneously in most dogs within 10 hours and all dogs within 24 hours of treatment. The results of the oral dosing study show if clinical signs consistent with amitraz toxicity had been demonstrated in the 1X, 3X, 5X safety studies, they would have been identified and differentiated from control dogs.

- iii. The formulation has tested positive as a dermal sensitizer. Possibly associated with this, total leukocyte counts were increased, 1.3 and 1.5-fold [relative to concurrent controls], respectively, for combined sexes at the 3X and 5X dose levels 24 hours postdose. Concurrently, neutrophils were increased 1.2-fold at the 3X and 1.5-fold at 5X.**

Monocytes were increased 24 hours postdose at 3X and 5X with [a] few elevated above expected ranges. An elevation in leukocyte counts is normally a response to infection.

The review points to the dermal sensitization noted on the standard guinea pig sensitization assay as a possible explanation for the observed elevations in WBC indices. It should be noted that this was a single dose study, so dermal sensitization is not a factor. Dermal irritation could be implicated, but Promeris was classified EPA category IV (mild or nonirritating) in the primary skin irritation study (MRID 46395809). In addition, skin irritation was not noted in study dogs. Slight elevations in WBC indices were noted in the 3X and 5X treatment groups in this study, but this pattern was not apparent in the puppy study (MRID 46401003) and in the repeated treatment study they were noted only in the 5X group and only at Day 30 (24 hours after the third treatment) with a slight increase in only the monocytes at Day 58. In both studies the increase in WBC indices was mild and transient. In addition, no signs of skin inflammation or sensitization were noted on examination of the application site in the repeated dose study when dogs were treated seven times at two-week intervals.

The reviewer states that an elevation in leukocyte count is "normally a response to infection". Elevated leukocyte counts can also occur with stress and non-infectious inflammatory processes. In the repeated treatment study the highest elevations in WBCs were noted in dogs with evidence of respiratory disease. The cause of the slight elevation in WBCs noted in other study dogs remains unclear. However, it should be noted that in

all studies...

Elevated WBCs were mild and transient. (The dog in the repeated treatment study with the largest elevations had signs of concurrent respiratory disease.)

The elevation in WBCs could not be tied to any clinical sign of illness (other than respiratory disease in one dog in the repeated treatment study).

Knowles et al. (Handbook of Pesticide Toxicology, Vol. 3 1991) reports amitraz is anti-inflammatory; therefore, it is unlikely that amitraz is causing an inflammatory response.

DEET has been reported to cause skin irritation in humans, however, skin irritation was not noted in study dogs. DEET is widely used in topical products, including products for direct human application.

iv. The increases in glucose and urea nitrogen levels for all dose groups (1X, 3X and 5X) at 24 hours are consistent with known effects of Amitraz, and indicate pharmacologically significant quantities of this active are absorbed at even the 1X dose level.

When comparisons were made using contemporaneous controls, slight increases in glucose were noted in 3X and 5X treated groups, but not in 1X groups. In the repeated treatment study, increases were noted only in the 5X group at Day 30 (24 hours following the third dose) and in the 3X and 5X groups at Day 58 (24 hours after the fifth dose). Glucose levels at these times were unaffected in some dogs and when elevated, differed only slightly from values measured pre-treatment and from values measured immediately prior to the applications. No increases in glucose were noted in any of the dogs treated with the 1X dose in any of the safety studies conducted with ProMeris.

Slight increases in BUN were observed, occurring in a non-dose dependent manner. In the repeat treatment study this was again observed. Three males and two females from all treatment groups slightly exceeded MPI historical controls at Day 58 and four males and four females from all treatment groups slightly exceeded MPI historical controls at Day 86. Renal histopathology was similar in treated and control dogs and confirmed a non-renal cause. Again, these changes were slight, transient and clearly not life-threatening

v. The proposed label suggests that this would be an over-the-counter product, readily available to dog owners, particularly as the only mention of veterinarians is in the standardized statements under the heading HAZARDS TO DOMESTIC ANIMALS ("Consult a veterinarian before using this product on aged, debilitated, medicated, pregnant or nursing animals. Individual sensitivities while rare may occur after the use of any pesticide product. If signs persist or become more severe, consult a veterinarian immediately...").

FDAH has no intention of offering this as an over-the-counter product. The product will

be marketed through veterinarians. Currently, we are not aware of any EPA process to reflect this in the product labeling.

- vi. **The label for Mitaban® (a formulation containing 19.9% Amitraz, approved by the FDA for treating generalized canine demodicosis) includes the following WARNING statement: "Toxicology studies conducted in the dog and other species suggest amitraz may alter the animal's ability to maintain homeostasis. Animals treated with MITABAN (Amitraz) should not be subjected to stress for a period of at least 24 hours posttreatment. Adverse reactions including three fatalities were reported during the clinical studies. In excess of 1100 patients with generalized demodicosis were topically treated with MITABAN." In addition, the Mitaban® label includes the statement: "Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian."**

The Mitaban label also includes "Ingestion of MITABAN may increase the risk of adverse effects. Therefore, appropriate care should be exercised both during and immediately after MITABAN application to minimize the opportunity for exposure by the oral route". The ProMeris formulation and method of application, including surface area exposed, differs considerably from those of Mitaban. Due to the application method (saturation of the entire dog), oral exposure from Mitaban is much more likely to occur.

- vii. **The overall exposure level to Amitraz associated with the proposed use of this product seems to be comparable to that associated with the use of Mitaban®. However, there are indications that Amitraz from the Promeris formulation is absorbed more rapidly and/or to a greater extent than Amitraz in the 250 ppm Mitaban-use dilution. Publically available information on Mitaban® includes the following [see myweb.cableone.net/bdturner/Mitaban.pdf]: "Blood glucose values were elevated at 4 hours posttreatment in the 250 ppm female group, and in both sexes at the 1250 and 2500 ppm concentrations. ...glucose values returned to normal within 24 hours posttreatment. In another study, groups of healthy beagles were topically treated with either 250 ppm, 750 ppm or 1250 ppm of active drug at 14 day intervals and for 12 weeks. Blood glucose values were elevated at the 750 ppm concentration at 4 hours posttreatment after 3 of 6 treatments, and after 5 of 6 treatments at the 1250 ppm level. In the 750 ppm group, serum glucose values returned to normal at 24 hours posttreatment, however for the 1250 ppm group, at 24 hours and after 3 of 6 treatments the levels remained significantly elevated." In the adult dog Promeris study [MRID 46401003] 1/6 of the 3X females and 5/6 5X females had elevated glucose levels (>120 mg/dL) at 24 hours, suggesting that Amitraz**

absorption from 5X Promeris treatment (7.0 mL) is greater than that from exposure to 2500 ppm Amitraz (or a 10X concentration of the use-dilution of Mitaban®), and a 1X (1.4 mL) Promeris treatment of an adult dog would then be associated with greater Amitraz absorption than that from exposure to a 2X (500 ppm Amitraz) use-concentration Mitaban® solution.

A single glucose measurement gives no indication as to the initiation, duration or magnitude of the glucose peak and nadir. However, it is concluded that amitraz absorption is greater from ProMeris treatment than from exposure to 2500ppm Mitaban based on the glucose values 24 hours posttreatment. The Mitaban and ProMeris glucose data discussed in the review can equally lead to a conclusion that rapid and extensive amitraz absorption with subsequent clearance occurs with Mitaban. It should be noted that the elevated glucose levels with Mitaban were consistently associated with clinical signs of sedation in a dose dependent manner. If this conclusion was correct, then clinical signs of amtraz toxicity as noted in dogs treated with 1250 and 2500ppm Mitaban should have been noted in ProMeris treated dogs. Such clinical signs were not observed in the single dose or the repeat dose studies.

There is repeated reference to amitraz "absorption". The primary exposure to toxic doses of amitraz with the use of Mitaban is oral. The product label specifically cautions that "ingestion of Mitaban may increase the risk of adverse effects". Results from oral dosing studies with amitraz in Mitaban documentation and the oral dosing safety study with Promeris confirms that oral exposure poses a much greater risk than 5X dermal exposure. This is confirmed by a plasma pharmacokinetic study conducted with ProMeris. Study 0817-C-FR-06-04 was conducted to measure the levels of R-28153 and amitraz in the blood of dogs following treatment with ProMeris at doses to provide 20 mg of each active/kg body weight. Multiple blood samples were taken the day of treatment and at intervals up to 56 days posttreatment. Amitraz was below the level of detection of the analytical method (3.2 ng/mL) in all but two of the 84 blood samples collected from the six dogs in the study. Amitraz was detectable, but not quantifiable (<50 ng/mL) in one sample collected from one dog 24 hours posttreatment and another dog 48 hours posttreatment. This confirms that essentially no amitraz is absorbed following the administration of ProMeris and what little absorption there is peaks 24 to 48 hours posttreatment.

viii. There is also potential for adverse drug reactions: from <http://www.aava.orci/rub/iatrogenic.html>: "Ivermectin which is in Heartgard heart worm preventative and is sometimes used to treat "mange" and ear mites, causes increases in monoamine neurotransmitter metabolites which could result in important adverse drug reactions with amitraz (Mitaban topical mange treatment)..." At the very least, if this product is registered it should be available only through licensed veterinarians, as is Mitaban®.

Is this reference to the off-label, unapproved, exaggerated dose of ivermectin ($\geq 200\mu\text{g}/\text{kg}$) commonly used to treat demodicosis or the approved dose use to prevent heartworm infection ($6\mu\text{g}/\text{kg}$)? The cited information is from a website that derives the concern from a purported talk given by Dr. Danny Scott, a veterinary dermatologist from Cornell University. The dose is not mentioned, but as a dermatologist Dr. Scott is likely referring to the exaggerated unapproved ivermectin dose that is sometimes used by veterinarians in combination with Mitaban for treating demodic mange. No publications were identified in a literature search by FDAH that indicates ivermectin causes increases in monoamine neurotransmitter metabolites nor were any documented reports of adverse reactions due to ivermectin/amitraz interaction.

The only reference found for concurrent use of high dose ivermectin therapy concurrently with amitraz saturation treatment (Uysal. 2001. Veteriner Fakultesi Dergisi 27: 2, 351-358) stated "For the treatment of the cases, ivermectin (ivomec) was administered subcutaneously to the animals at a dose of $0.4\text{ mg}/\text{kg}$ the dosage was repeated weekly in a total of 3 injections. A series of 5-6 treatments with amitraz (kenaz 12.5% EC) were also applied topically at 3-day intervals. All (100%) of the dogs responded and recovered." No adverse reactions were reported.

As previously noted, FDAH intends to market the product through veterinarians.

- 2. The companion animal safety study in MRID 46401004, conducted on 8-week old puppies, also does not demonstrate an adequate (5X) margin of safety for the proposed use. The greatest concern involves the death of 3X female #122, sacrificed in extremis on Day 9. This animal had a urea nitrogen of $8\text{ mg}/\text{dL}$ pretest, $22\text{ mg}/\text{dL}$ at 24 hours postdose, and $33\text{ mg}/\text{dL}$ at 8 days postdose, as well as an elevated serum potassium level at 24 hours, consistent with known effects of Amitraz. While no deaths occurred in 5X puppies, female #122 may have been representative of a more sensitive population subgroup. In addition, 1X puppy #125 was found dead on Day 9. While this puppy had shown a substantial weight loss (from 2.01 to 1.82 kg) in the preexposure period from Day -4 to -1, the possibility that exposure to Amitraz may have contributed to death cannot be ruled out. Increases in blood urea nitrogen (BUN) and a dose-related trend of increasing incidences (Placebo: 1/12; 1X: 2/12; 3X: 3/12; 5X: 5/12) of elevated glucose ($>120\text{ mg}/\text{dL}$) at 24 hours postexposure indicate that physiologically significant amounts of Amitraz had been absorbed,**

The one animal death occurred in the 3X treatment group. The lack of a dose-related effect on deaths is discounted; the review states that the animal that was euthanized "may have been representative of a more sensitive population subgroup". The pups in this study were all Covance bred beagles. Several littermates were included in the study.

Thus, "subgroup" genetics is unlikely.

The review states that there was a "dose-related trend of increasing incidences of elevated glucose at 24 hours postexposure". No trends of increasing glucose were noted either statistically or numerically. As expected in young fasted dogs, glucose values were quite variable at all time points. This conclusion is based on the rejection of the pre-treatment values (which were high), the arbitrary assignment of > 120 mg/dl as a determinant of hyperglycemia and an apparent disregard of glucose values measured at later time points which tended to be elevated in the controls. These are readily apparent on examination of the individual profile plots. The arbitrary assignment of >120 mg/dl is not consistent with pretreatment glucose values (65-156 mg/dl) and is not consistent with MPI historical values for beagle pups 0-3 months of age (73 to 126 mg/dl). Thus, the conclusions are not supported if appropriate contemporaneous controls are used for comparison. In the repeated treatment study, elevated glucose was not observed when test subjects were young. As dogs aged in this study glucose values did become elevated reaching significance in 5X at Day 30 and at 3X and 5X at Day 58. Thus, it appears that hyperglycemia does not occur in young pups.

3. Refer to the executive summaries for MRIDs 46401003 and 46401004 for additional comments and conclusions regarding TRB's reviews of these studies.

On page 35, the review states "At 24 hours postdose incidences of glucose >120 mg/dL showed a clear dose response (Placebo group: 1/12; 1X group: 2/12; 3X: 3/12; 5X: 5/12),..." As mentioned previously, comparisons to contemporary control data are more valid than are comparisons to reference values generated at an unrelated laboratory. The incidences quoted are based on an arbitrary selection of 120 mg/dl as the determinant for elevated glucose. If a similar analysis is conducted using either pretreatment values or comparisons with contemporaneous controls, there are no increases in blood glucose.

The review also states "...and the results are striking in comparison with Day 8 and Day 22 incidences (no more than 1/12 per group)." According to MPI historical controls and clinical pathology literature, range values for glucose decrease with increasing age, with changes evident between 3 and 4 months of age. Therefore one would expect declining glucose values in pups that are approximately 12 weeks of age (on Day 22) versus pups that are approximately 9 weeks of age (on Day 8). Therefore the comparison of Day 8 data versus Day 22, data rather than comparisons to contemporaneous controls, and the subsequent conclusions, are not valid.

The review also states "The relatively high glucose levels at Week -1 suggest the possibility that at least some of the puppies may not have [sic] been adequately fasted at that time before blood collection." Study documents reveal no indication of inadequate fasting prior to blood sampling in this GLP study. There is no reason to discount the observation. Furthermore, large variances in blood glucose are to be expected in young puppies.

The review continues, "A dose-related hyperglycemic effect in puppies at 24 hours postdose would be consistent with what was observed in adult dogs (MRID 46401003)." Though true, there is no scientifically sound evidence suggesting that hyperglycemia occurs in puppies treated with ProMeris. This lack of hyperglycemic effect was confirmed in the repeated treatment study wherein elevated blood glucose was not observed early in the study when test subjects were young, but mildly elevated glucose was observed in 5X treated pups after the subjects reached approximately 15 weeks of age.

On page 38, discussing the serum potassium level for puppy # 122 (euthanized), the Reviewer states "The serum potassium level at 24 hours (6.7 mEq/L) was the highest post-exposure value...". It should be noted that one female had a pre-exposure value of 6.8 mEq/L. These values are consistent with MPI historical controls.

On page 39 the review states "While there were some cases in which there were no significant differences between controls and test material treated groups at 24 hours, there were significant differences between pretreatment and 24-hour postdose values, suggesting the possibility of pharmacological activity involving one or more of the inerts". Similar references to significant differences between pre-dose and post-dose values are made elsewhere as well. This is curious because the Study Director and FDAH did not do statistical comparisons between predose and postdose values. How was this determined; by statistical analysis conducted by EPA or are differences noted merely numerical?

Additional data

In addition to the studies reviewed by EPA and the studies cited earlier in this reply, a study (Study 0817-C-SA-02-04) has been conducted by a laboratory in South Africa evaluating the safety of ProMeris in Chihuahuas, a breed of dog contraindicated on the labels of many products containing amitraz because of its reported sensitivity to amitraz. The dogs in this study were 8 weeks of age and older, and ranged from 0.55 to 2.2 kg in body weight. Six dogs were dosed twice (Study Days 0 and 14) with 0.67 mL of ProMeris. This resulted in doses ranging from 49 to 183 mg/kg body weight each of metaflumizone and amitraz. Six dogs served as untreated controls. Parameters evaluated included clinical signs, body weights, food consumption, physical and neurological examinations (including heart rate and body temperature) and numerous blood clinical chemistry and hematological measurements at various intervals following each dosing. While there were some statistically significant differences between treated and control groups in a few clinical chemistry and hematological parameters, primarily on Day 1, these differences were not considered biologically significant by the Study Director. He concluded that ProMeris was safe for use as recommended in Chihuahuas.

Appendix A

**Summaries of Additional Target Animal Safety and Pharmacokinetic Studies with
ProMeris**

Study 0817-C-US-12-04, conducted by MPI Research Inc., Mattawan, Michigan, U.S.A.

Design: This study was designed to evaluate the safety of repeated treatment with ProMeris Spot-On for Dogs (15% w/v metaflumizone and 15% w/v amitraz spot-on) in 10-week old puppies. Sixteen male and sixteen female ten-week-old beagle puppies were ranked by weight within gender, blocked into groups of four and randomly assigned to four treatment groups. At the time of first treatment, males weighed 2.00 to 4.36 kg and females weighed 2.06 to 3.65 kg. The four groups were treated with ProMeris Spot-On administered at approximately 1X, 3X, or 5X the proposed recommended dose or a Placebo Control comprised of ProMeris Spot-On inert ingredients applied at 5X volume as indicated below. Treatments were applied at 14-day intervals, during a 14-week study. This frequency of application is approximately twice that expected under commercial use conditions and was chosen as a worse case scenario.

Group	Males	Females	Dose Volume			Metaflumizone/Amitraz		
			(mL/ ≤5.0 kg)	(mL/5.1-1 0.0 kg)	(mL/10.1- 25.0 kg)	(mg/ ≤5.0 kg)	(mg/5.1-1 0.0 kg)	(mg/10.1- 25.0 kg)
Placebo								
Control	4	4	3.4	6.7	16.7	0	0	0
1X	4	4	0.7	1.4	3.4	105	210	510
3X	4	4	2.1	4.0	10.0	315	600	1500
5X	4	4	3.4	6.7	16.7	510	1005	2505

The test and control substances were applied topically along the dorsal midline between the scapula. Daily observations for mortality, clinical signs, and food consumption and body weight measured at regular intervals were conducted throughout the study. Additionally, on each treatment day, puppies were examined prior to treatment and at 5 to 15 minutes, 1, 2, 3, and 10 hours posttreatment. All puppies received physical and neurological examinations (including heart rate and body temperature) prior to each dosing, at 4 hours postdosing, the day after each dosing, and 7 days after each dosing. Heart rate and body temperature were also recorded 10 hours following each treatment. Blood and urine for hematology, coagulation, clinical chemistry and urinalysis were collected once pretreatment, the day after each dose, and 7 days after dose for treatments 1, 3, 5, and 7. Ninety-seven days after the initial treatment gross necropsy examinations were performed and organ weights recorded for two animals per gender per treatment group. Complete microscopic examinations were performed on animals from the Placebo Control and 5X treated groups and renal histology performed on necropsied animals from the 1X and 3X treated groups.

Results: Exaggerated and repeated treatment with ProMeris Spot-On for Dogs at 1X, 3X and 5X the proposed recommended dose had no effect on clinical findings, heart rates, body weight, body weight changes, food consumption, physiological/neurological examinations, macroscopic necropsy observations, organ weights, and microscopic observations. Transitory salivation occurring immediately post dosing was noted on some treatment days in a small number of animals from all groups, including Placebo

Controls. Since this observation was noted in both ProMeris Spot-On treated and Placebo Control treated dogs it was not considered an effect of the active ingredients, metaflumizone or amitraz. This reaction is more likely an effect of treatment application. Clinically insignificant lower body temperature was noted primarily in 3X and 5X treated groups at several intervals during the study. These changes were usually noted on treatment days following dose administration or on the day after a treatment. The 5X group was most frequently affected. A summary of significant ($p < 0.1$) body temperature data is presented in Table 1 below.

Several hematology and clinical chemistry parameters did reach statistical significance ($p < 0.1$) but most were neither physiologically relevant nor dose-dependent and were not considered the result of treatment with ProMeris Spot-On. Notable hematology parameters included leukocytes, neutrophils and monocytes that tended to be variably increased in 5X treated animals from Day 28 though Day 58. Increases were primarily due to values from one male and one female that tended to be consistently elevated, with other animals only sporadically elevated. The female had a clinically apparent respiratory illness that was associated with the increased number of these cells and as such was not considered ProMeris Spot-On related. Similar to the leukocytes, fibrinogen tended to be variably elevated in 5X treated individuals, including the female with respiratory illness, at intervals between Day 2 and Day 58. Urea nitrogen was very slightly increased (< 1.27 fold) at all dose levels, occurring on posttreatment Days 58 and 86. Increased urea nitrogen was not dose dependent, not associated with a corresponding increase in creatinine or with renal histopathology, suggesting a non-renal cause. It was not considered toxicologically significant. Glucose was increased ≤ 1.27 fold in 3X and 5X treated animals on Days 30 and 58, one day following the 3rd and 5th doses. Summaries of clinical pathology parameters that were significantly different from control ($p < 0.1$) and possibly biologically relevant are presented in Table 2 and Table 3 below. There was no treatment-related pattern to results of urinalysis.

One 3X treated male was euthanatized *in extremis* 2 days after treatment. This animal had watery feces that were observed just prior to treatment. Ten hours posttreatment, pale oral mucous membranes were first noted. At 24-hours posttreatment, activity was at first increased and then decreased with black and watery feces, ataxia, dilated pupils and inappetence. At 48-hours posttreatment signs progressed to extremis necessitating euthanasia. Full hematology and clinical chemistry, measured 24-hours posttreatment, indicate hypoalbuminemia, hypoproteinemia, hyponatremia, hypokalemia and hypoglycemia. All are consistent with the diarrhea noticed pre-and post-treatment. Full necropsy was performed and the only macroscopic observation noted for this animal was a small, incidental, endocardial cyst in the right ventricle. Numerous microscopic observations were seen. Within the liver there was diffuse, mild hepatocellular vacuolation, possibly the result of clinically apparent inappetence, minimal single cell necrosis, and minimal Kupffer cell hypertrophy/hyperplasia. Mild lymphoid depletion was noted in the spleen and thymus, possibly the result of stress. Coccidia were present in the small intestine but there was no evidence of enteritis. No definitive cause of death could be determined for this puppy, but the death could not be attributed to treatment.

Table 1.

Summary of Significant (p<0.1) Body Temperature Data							
Parameter	Sex	Day	Dosage Level Increase (+) /Decrease (-)	Treated Group		Placebo Control	
				Mean	SD	Mean	SD
Body Temperature							
	Pooled	1 (10 hr) ¹	5X(+)	38.66	0.393	38.36	0.169
	Pooled	8	3X(-)	38.11	0.168	38.29	0.387
	Pooled	15 (4 hr) ²	5X(-)	38.21	0.236	38.58	0.271
	Pooled	57 (10 hr) 1	5X(-)	38.24	0.192	38.56	0.119
	Pooled	72	5X(-)	38.38	0.311	38.60	0.393
	Pooled	86	1X(-)	38.74	0.160	39.15	0.431
	Pooled	86	3X(-)	38.61	0.358		
	Pooled	86	5X(-)	38.33	0.320		
¹ 10 hour postdose ² 4 hour postdose SD – Standard Deviation Treatments were administered on Days 1, 15, 29, 43, 57, 71 and 85.							

Table 2.

Summary of Significant and Biologically Relevant Hematology Data							
Parameter	Sex	Day	Dosage Level Increase (+) /Decrease (-)	Treated Group		Placebo Control	
				Mean	SD	Mean	SD
Leukocytes	Pooled	Day 30	5X(+)	15.93	4.652	12.89	1.669
Fibrinogen	Pooled	Day 2	5X(+)	342.3	64.00	262.9	38.48
	Pooled	Day 30	5X(+)	265.0	60.13	210.6	38.08
	Pooled	Day 56	5X(+)	281.3	88.32	214.3	56.77
	Pooled	Day 58	5X(+)	286.4	76.17	211.0	44.87
Neutrophils	Pooled	Day 30	5X(+)	10.993	4.8138	8.250	1.2981
Monocytes							

Pooled	Day 30	5X (+)	0.958	0.2588	0.623	0.2104
Pooled	Day 58	5X (+)	1.485	1.6605	0.549	0.2774

SD – Standard Deviation

Treatments were administered on Days 1, 15, 29, 43, 57, 71 and 85. Samples were collected prior to, 24 hours post and 7 days following treatments administered on Day 1, 29, 57 and 85.

Table 3.

Summary of Significant (p<0.1) and Biologically Relevant Clinical Chemistry Data							
Parameter	Sex	Day	Dosage Level Increase (+) /Decrease (-)	Treated Group		Placebo Control	
				Mean	SD	Mean	SD
Urea Nitrogen							
	Pooled	Day 58	1X (+)	15.3	3.54	11.6	1.92
	Pooled	Day 58	3X (+)	18.1	3.44		
	Pooled	Day 58	5X (+)	15.9	3.44		
	Pooled	Day 86	1X (+)	16.4	3.16	13.3	2.82
	Pooled	Day 86	3X (+)	19.3	4.96		
	Pooled	Day 86	5X (+)	17.6	3.29		
Glucose							
	Pooled	Day 30	5X (+)	129.3	26.90	108.0	8.99
	Pooled	Day 58	3X (+)	111.4	15.28	96.4	7.44
	Pooled	Day 58	5X (+)	122.5	15.83		

SD – Standard Deviation

Treatments were administered on Days 1, 15, 29, 43, 57, 71 and 85. Samples were collected prior to, 24 hours post and 7 days following treatments administered on Day 1, 29, 57 and 85.

Conclusion: Repeated administrations of 1X, 3X and 5X the recommended dose of ProMeris Spot-On for Dogs, given to mimic a full season of treatment in dogs beginning at 10 weeks of age, resulted in no substantial deleterious effects and is safe for use according to label recommendations.

Study 0817-C-US-14-04, conducted by MPI Research Inc., Mattawan, Michigan, U.S.A.

Design: This study was designed to evaluate the safety of ProMeris Spot-On for Dogs following inadvertent oral exposure from auto- or allo-grooming. Eight male and eight female young adult beagle dogs were ranked by weight within gender, blocked into groups of two and randomly assigned to two treatment groups. Males weighed 6.40 to 7.74 kg and females weighed 5.16 to 5.87 kg. One treatment group received 10% the proposed recommended dose of ProMeris Spot-On for Dogs, a volume of 0.14 mL, applied to the tongue as an estimate of the maximum anticipated oral exposure from grooming. The other group received similar treatment with 0.9% bacteriostatic sodium chloride for injection, USP, at the same dose volume as indicated in the following table:

Group	Males	Females	Dose	Metaflumizone/Amitra
			Volume	z
			(ml/5.0-9.9 kg)	(mg/5.0-9.9kg)
Control	4	4	0.14	0
Metaflumizone/Amitraz	4	4	0.14	21/21

Daily observations for mortality, clinical signs and food consumption, and body weight measurements, physical and neurological examinations (including heart rate and body temperature) at regular intervals, were conducted prior to treatment and for seven days posttreatment. On the day of treatment, dogs were examined prior to treatment, at 5 to 15 and 30 to 45 minutes, and hourly through 10 hours posttreatment. Blood samples were collected prior to treatment, the day after treatment and at study conclusion 7 days after treatment for evaluation of hematology, coagulation, and clinical chemistry parameters.

Results: All dogs survived to study conclusion. ProMeris Spot-On for Dogs administered orally at 10% the proposed recommended dose had no effect on mortality, body weight, food consumption, neurological examinations, or clinical pathology parameters.

At dosing, avoidance behaviors including spitting, head shaking, and salivation were noted in all ProMeris Spot-On treated dogs. Beginning one to two hours posttreatment, decreased activity, slightly reduced body temperature and pale oral mucous membranes were noted in some ProMeris Spot-On treated animals. Ataxia resolving within 4 hours posttreatment was noted in one female. Normal activity returned for all dogs within 10 hours posttreatment.

Conclusion: Oral treatment with 10% the recommended topical dose of ProMeris Spot-On for Dogs has no lasting deleterious effects and is safe for use according to label recommendations.

Study 0817-C-SA-02-04, conducted by ClinVet International (Pty) Ltd., Bloemfontein, South Africa

Design: This study was designed to evaluate the safety of two treatments of ProMeris Spot-On for Dogs administered in toy breed dogs. Twelve Chihuahuas, 10 males and two females all over 8 weeks of age, were ranked by weight within gender, blocked into groups of two and randomly assigned to two treatment groups of six dogs each. Males weighed 0.55 to 2.20 kg and the two females weighed 1.5 and 1.55 kg on Day -1. On Day 0, one group was treated with 0.67 mL ProMeris Spot-On for Dogs, applied to the skin between the shoulder blades. The other group served as untreated control. Treatment was repeated on Day 14.

Group	Males	Females	Dose Volume (mL/Dog)	Metaflumizone/Amitraz mg
Control	5	1	0	0
Metaflumizone/Amitraz	5	1	0.67	100.5/100.5

The dogs were observed daily for general signs of health and weighed periodically throughout the study. Clinical examinations were performed on all animals on Days -1, 3, 14 (before the second treatment), 17 and 21. The dogs were observed regularly the day of and the day after each treatment for signs of intolerance to treatment. In addition, the dogs were observed on Days 2, 7, 16 and 21 for signs of local intolerance. Blood for hematology and clinical chemistry was collected the day prior to treatment and one and seven days following each treatment.

Results: The administration of 0.67 mL of ProMeris Spot-On for Dogs resulted in doses ranging from 49 mg/kg to 183 mg/kg body weight each of metaflumizone and amitraz. Chihuahuas treated twice at these dose levels maintained or gained body weight during the study. Transitory signs of hyperactivity and localized pruritis at the application site were noted in four of six treated dogs, primarily within the first hour following treatment. The Study Director concluded that the presence of a liquid on the skin was probably the cause of these reactions. Lacrimation was noted in one dog within minutes after the second treatment and vomiting was noted the day after each treatment for one dog. A small subcutaneous swelling, approximately 7 mm x 7 mm x 7 mm, was noted at the application site of each of three dogs at 2, 4 and 11 days posttreatment, respectively. These swellings regressed during the course of the study and had disappeared by Day 21. The Study Director noted that the swellings resembled injection site reactions and as all the dogs were vaccinated against Rabies and received prophylactic injections of Imidocarb 15 days before the start of the study, this may be a likely explanation.

There were significant differences ($p < 0.10$) between treated and control groups for six of 13 hematological and three of 18 clinical chemistry parameters the day after the first treatment, but most were not physiologically relevant. It should be noted that white blood cell count was higher in the treated dogs compared to controls, but the values for

all dogs were within reference ranges. Very mild, acute increases in white cell count have been observed in other formal safety studies with ProMeris Spot-On for Dogs and are thought to be due to a slight, transient inflammatory response. There were no differences in the same 31 parameters evaluated at the other time points (Days 7, 15 and 21) except for a very small, irrelevant difference between groups in glucose on Day 21.

Conclusion: ProMeris Spot-On for Dogs administered at the dose of 0.67 mL to Chihuahua dogs with body weights between 0.55 and 2.05 kg is well tolerated and is safe for use according to label recommendations.

Study 0817-C-FR-06-04, conducted by Avogrado, Fontenilles, France

Design: This study was designed to evaluate the pharmacokinetics of ProMeris Spot-On for Dogs in dog plasma. ProMeris Spot-On was administered to six Beagle dogs, three males and three females, at 0.13 mL/kg body weight to provide the minimum proposed commercial dose of 20 mg of each active/kg body weight. The product was applied at a single spot between the shoulder blades. Plasma samples were collected approximately 5 and 10 hours and at 1, 2, 3, 5, 7, 10, 14, 21, 28, 42 and 56 days posttreatment. The plasma was analyzed for both metaflumizone and amitraz using a validated HPLC method with Limits of Quantification (LOQ) of 50 ng/mL for both metaflumizone and amitraz.

Results: The results of this study are shown in Tables 1 and 2 for metaflumizone and amitraz, respectively. Metaflumizone was detectable (>1 ppb), but generally not quantifiable (<50 ppb) until 28 (3 of 6 dogs) and 42 days (4 of 6 dogs) posttreatment. One dog also had measurable levels at 7, 10 and 14 days and 2 dogs at 21 days. Levels in the plasma were generally below 100 ppb, and quite low compared to previously reported levels in the hair in the range of 300 ppm. There was a trend for males to have higher levels than females, but all values were too low to be of interest. Amitraz was essentially not detectable (<3.2 ppb) in the plasma over the 56 day study; only 2 samples (out of the total of 84) had detectable, but not quantifiable levels (<50 ppb). The levels of both R-28153 and amitraz were too low in plasma in this study to allow the calculation of standard pharmacokinetic parameters (C_{max} , AUC, etc.).

Conclusions: Metaflumizone is poorly absorbed when applied to dogs in the ProMeris Spot-on formulation, reaching peak levels 28 to 42 days posttreatment. The amitraz in Promeris is essentially not detectable in the blood of dogs.

Appendix B

Historical Control Clinical Pathology Data from MPI Laboratories

80490-E

DP D319379

Page _____ is not included in this copy.

Pages 24 through 27 are not included in this copy.

The material not included contains the following type of information:

- Identity of product inert ingredients.
- Identity of product impurities.
- Description of the product manufacturing process.
- Description of quality control procedures.
- Identity of the source of product ingredients.
- Sales or other commercial/financial information.
- A draft product label.
- The product confidential statement of formula.
- Information about a pending registration action.
- FIFRA registration data.
- The document is a duplicate of page(s) _____.
- The document is not responsive to the request.
- Internal deliberative information.
- Attorney-Client work product.
- Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

[PACKAGE INSERT LANGUAGE]

Promeris Spot On for Dogs

Single spot application for control of fleas and ticks on dogs and puppies over eight weeks of age.

ACTIVE INGREDIENTS:

Metaflumizone (CAS No. 35037-73-1).....	14.34%
Amitraz (CAS No. 33089-61-1).....	14.34%
OTHER INGREDIENTS.....	71.32%
TOTAL.....	100.00%

KEEP OUT OF REACH OF CHILDREN CAUTION

READ ENTIRE LABEL BEFORE EACH USE

For control of fleas and ticks on dogs and puppies over eight weeks of age. *Promeris Spot On for Dogs* is a convenient single spot application, provides rapid control of existing flea and tick infestations and protects against reinfestation. Rapidly kills adult fleas which may cause flea allergy dermatitis. Controls brown dog ticks, American dog ticks, lone star ticks, and black legged or deer ticks, which can transmit Lyme disease. The effectiveness of a single application of *Promeris Spot On for Dogs* persists for at least one month in controlling both fleas and ticks. It may also be used to prevent infestation in flea free animals being taken into a flea contaminated environment. Apply a single dose prior to exposure for one month of protection. Therefore, monthly application is recommended to provide continuous effective control of fleas and ticks and prevent reinfestation.

Promeris Spot On for Dogs contains two active ingredients, including metaflumizone which provides a high level of control of fleas by blocking gated sodium channels, and amitraz which provides rapid and lasting control of ticks. This product resists the effects of water and remains effective even if the dog is exposed to sunlight. The benefits of *Promeris Spot On for Dogs* include:

- Kills adult fleas which may cause flea allergy dermatitis
- Kills brown dog ticks, American dog ticks, lone star ticks and black legged or deer ticks which can transmit Lyme disease
- Fast acting
- Full month protection with a single treatment
- Prevents reinfestation with fleas and ticks
- Waterproof
- Easy to use applicator
- Effective on the dogs indoors and/or outside

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. For external use on dogs and puppies over eight weeks of age. Do not use on any other animals.

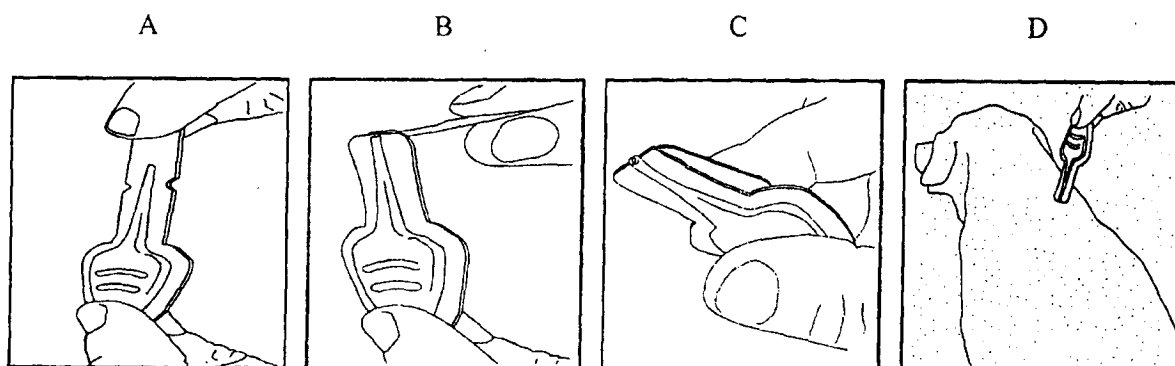
HOW TO SUPPLY:

Promeris Spot On for Dogs is available in 5 packaging presentations for different body weights of dogs and puppies over 8 weeks old (see Table below). Each package contains six individual applicator tubes to provide six monthly treatments. The animal body weight limits and product volume sizes are specified on individual labels of cartons, foil pouches and applicators.

Dog Size (lb)	Dog Size (kg)	fl. oz/Applicator	mL/Applicator
≤ 11	≤ 5	0.023	0.67
11-22	5-10	0.045	1.33
22-56	10-25	0.113	3.33
56-89	25-40	0.180	5.33
89-111	40-50	0.225	6.66

HOW TO APPLY:

1. Remove one applicator from the package.
2. Use two hands to hold both ends of applicator with tip end pointing up and away from face and body (Figure A).
3. Bend the applicator backward to break the tip along the fracture line (Figure B).
4. Hold opened applicator with a single hand with the tip end folded back against the body of applicator (Figure C). Avoid touching opened tip.
5. Push the opened tip through dog's hair onto skin between the shoulder blades. Squeeze applicator to expel the entire content to dog's skin (Figure D). Do not apply on the surface of dog's hair. Avoid contacting treated area until dry.
6. Place used applicator in trash.



STORAGE AND DISPOSAL

Do not contaminate water, food, or feed by storage or disposal.

PESTICIDE STORAGE: Store in a cool dry place.

CONTAINER DISPOSAL:

If empty: Do not reuse this container. Place in trash or offer for recycling if available.

If partly filled: Call your local solid waste agency for disposal instruction. Never place unused product down any indoor or outdoor drain.

**KEEP OUT OF REACH OF CHILDREN
CAUTION**

FIRST AID	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment.	
If swallowed	<ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by the poison control center or doctor.• Do not give anything by mouth to an unconscious person.
If inhaled	<ul style="list-style-type: none">• Move person to fresh air.• If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably by mouth-to-mouth, if possible.• Call a poison control center or doctor for further treatment advice.
If in eyes	<ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes.• Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice.
If on skin or clothing	<ul style="list-style-type: none">• Take off contaminated clothing.• Rinse skin immediately with plenty of water for 15-20 minutes.• Call a poison control center or doctor for treatment advice.

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS. CAUTION

Harmful if swallowed, inhaled or absorbed through skin. Causes moderate eye irritation. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Avoid breathing vapor. Avoid contact with eyes, skin or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before use.

HAZARDS TO DOMESTIC ANIMALS

For external use only. For use on dogs only. Do not use on cats or any animals other than dogs. Do not use on puppies under eight weeks of age. Consult a veterinarian before using this product on aged, debilitated, medicated, pregnant or nursing animals. Individual sensitivities while rare may occur after the use of any pesticide product. If signs persist or become more severe, consult a veterinarian immediately. For further product information call 1-800-477-1365.

PHYSICAL AND CHEMICAL HAZARDS

Combustible. Do not use or store near heat or open flame.

LIMITED WARRANTY AND DISCLAIMER

Recommendations for use of this product are based upon tests believed to be reliable. The use of this product being beyond control of the seller, no guarantee, express or implied, is made as to the effects of such use or the results to be obtained if not used in accordance with printed directions and established safe practice. Buyer's exclusive remedy and seller's exclusive liability for any and all claims, losses, damages or injuries resulting from the use or handling of this product, whether or not based in contract, negligence, strict liability in tort or otherwise shall be limited, at the seller's option to replacement of, or the repayment of the purchase price for, the quantity of product with respect to which damages are claimed.

EPA Reg. No. 80490-
EPA Est. No.

Manufactured For:
Fort Dodge Animal Health
P.O. Box 5366
Princeton, NJ 08543-5366

[CARTON LANGUAGE – FRONT PANEL]

Promeris Spot On for Dogs

SINGLE SPOT APPLICATION FOR CONTROL OF FLEAS AND TICKS ON DOGS AND PUPPIES OVER EIGHT WEEKS OF AGE.

For Dogs XX-XX lbs.

ACTIVE INGREDIENTS:

Metaflumizone (CAS No. 35037-73-1)	14.34%
Amitraz (CAS No. 33089-61-1)	14.34%
OTHER INGREDIENTS	<u>71.32%</u>
TOTAL	100.00%

Contains 6 – XX fl oz (XX mL) applicators

KEEP OUT OF REACH OF CHILDREN CAUTION

For first aid and additional precautionary statements, refer to product package insert.

[Note: Five different packages (0.67, 1.33, 3.33, 5.33 and 6.66 mL/applicator) are available for various sizes of dogs. The XX lb dog body weight, XX fl oz and XX mL will be printed on the carton for each appropriate packaging size.]

[CARTON LANGUAGE - BACK PANEL]

Promeris Spot On for Dogs

Promeris Spot On for Dogs is a convenient single spot application, provides rapid control of existing flea and tick infestations and protects against reinfestation.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. See inside pamphlet for additional directions for use. Read the entire label and enclosed directions before using the product. For use on dogs only.

For control of fleas and ticks, apply the contents of the applicator tube to a single spot on the skin of the dog between the shoulder blades. Remove the applicator tube from the package and holding the tube upright, bend the tip of the tube to break the tip along the fracture line. The top of the tip will fold back against the tube. Push the tip of the applicator tube through the dog's hair to the skin surface and squeeze the tube to expel the entire contents. Do not apply the product to the surface of the dog's coat. Monthly application is recommended to provide continuous effective control of fleas and ticks and prevent reinfestation.

EPA Reg. No. 80490-
EPA Est. No. XXX

Manufactured For:
Fort Dodge Animal Health
P.O. Box 5366
Princeton, NJ 08543-5366

Net Contents:

[FOIL CONTAINER LABEL LANGUAGE]

Promeris Spot On for Dogs

(14.34% Metaflumizone & 14.34% Amitraz)

FOR DOGS AND PUPPIES OVER EIGHT WEEKS OF AGE.
For Dogs XX-XX lbs.

**KEEP OUT OF REACH OF CHILDREN.
CAUTION**

How to apply: See "DIRECTIONS FOR USE" in the product package insert.

EPA Reg. No. 80490-

EPA Est. No. XXX

Lot No.

Contains XX fl oz (XX mL)

[APPLICATOR LABEL LANGUAGE]

Promeris Spot On for Dogs
(14.34% Metaflumizone & 14.34% Amitraz)

FOR DOGS AND PUPPIES OVER EIGHT WEEKS OF AGE.

For Dogs XX-XX lbs.

KEEP OUT OF REACH OF CHILDREN.

CAUTION

See product package insert for additional directions.

EPA Reg. No. 80490-

EPA Est. No. XXX-

Lot No.

Contains XX fl oz (XX mL)

[PACKAGE INSERT LANGUAGE]

Promeris Spot On for Dogs

Single spot application for control of fleas and ticks on dogs and puppies over eight weeks of age.

ACTIVE INGREDIENTS:

Metaflumizone (CAS No. 35037-73-1).....	14.34%
Amitraz (CAS No. 33089-61-1).....	14.34%
OTHER INGREDIENTS	71.32%
TOTAL	100.00%

**KEEP OUT OF REACH OF CHILDREN
CAUTION**

READ ENTIRE LABEL BEFORE EACH USE

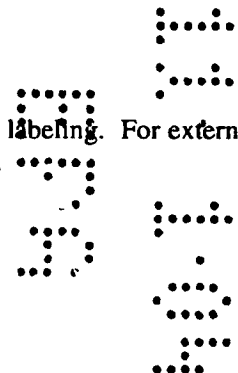
For control of fleas and ticks on dogs and puppies over eight weeks of age. *Promeris Spot On for Dogs* is a convenient single spot application, provides rapid control of existing flea and tick infestations and protects against reinfestation. Rapidly kills adult fleas which may cause flea allergy dermatitis. Controls brown dog ticks, American dog ticks, lone star ticks, and black legged or deer ticks, which can transmit Lyme disease. The effectiveness of a single application of *Promeris Spot On for Dogs* persists for at least one month in controlling both fleas and ticks. It may also be used to prevent infestation in flea free animals being taken into a flea contaminated environment. Apply a single dose prior to exposure for one month of protection. Therefore, monthly application is recommended to provide continuous effective control of fleas and ticks and prevent reinfestation.

Promeris Spot On for Dogs contains two active ingredients, including metaflumizone which provides a high level of control of fleas by blocking gated sodium channels, and amitraz which provides rapid and lasting control of ticks. This product resists the effects of water and remains effective even if the dog is exposed to sunlight. The benefits of *Promeris Spot On for Dogs* include:

- Kills adult fleas which may cause flea allergy dermatitis
- Kills brown dog ticks, American dog ticks, lone star ticks and black legged or deer ticks which can transmit Lyme disease
- Fast acting
- Full month protection with a single treatment
- Prevents reinfestation with fleas and ticks
- Waterproof
- Easy to use applicator
- Effective on the dogs indoors and/or outside

DIRECTIONS FOR USE

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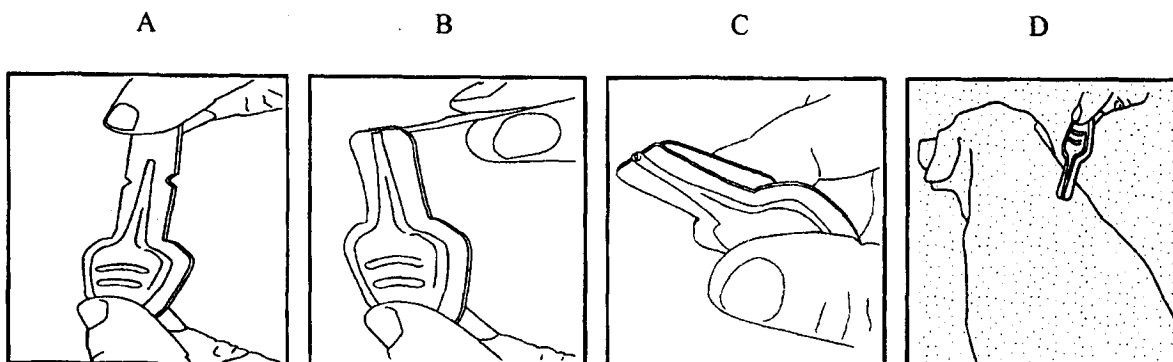
HOW TO SUPPLY:

Promeris Spot On for Dogs is available in 5 packaging presentations for different body weights of dogs and puppies over 8 weeks old (see Table below). Each package contains six individual applicator tubes to provide six monthly treatments. The animal body weight limits and product volume sizes are specified on individual labels of cartons, foil pouches and applicators.

Dog Size (lb)	Dog Size (kg)	fl. oz/Applicator	mL/Applicator
≤ 11	≤ 5	0.023	0.67
11-22	5-10	0.045	1.33
22-56	10-25	0.113	3.33
56-89	25-40	0.180	5.33
89-111	40-50	0.225	6.66

HOW TO APPLY:

1. Remove one applicator from the package.
2. Use two hands to hold both ends of applicator with tip end pointing up and away from face and body (Figure A).
3. Bend the applicator backward to break the tip along the fracture line (Figure B).
4. Hold opened applicator with a single hand with the tip end folded back against the body of applicator (Figure C). Avoid touching opened tip.
5. Push the opened tip through dog's hair onto skin between the shoulder blades. Squeeze applicator to expel the entire content to dog's skin (Figure D). Do not apply on the surface of dog's hair. Avoid contacting treated area until dry.
6. Place used applicator in trash.



STORAGE AND DISPOSAL

Do not contaminate water, food, or feed by storage or disposal.

PESTICIDE STORAGE: Store in a cool dry place.

CONTAINER DISPOSAL:

If empty: Do not reuse this container. Place in trash or offer for recycling if available.

If partly filled: Call your local solid waste agency for disposal instruction. Never place unused product down any indoor or outdoor drain.

**KEEP OUT OF REACH OF CHILDREN
CAUTION**

FIRST AID	
Have the product container or label with you when calling a poison control center or doctor, or going for treatment.	
If swallowed	<ul style="list-style-type: none">• Call a poison control center or doctor immediately for treatment advice.• Have person sip a glass of water if able to swallow.• Do not induce vomiting unless told to do so by the poison control center or doctor.• Do not give anything by mouth to an unconscious person.
If inhaled	<ul style="list-style-type: none">• Move person to fresh air.• If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably by mouth-to-mouth, if possible.• Call a poison control center or doctor for further treatment advice.
If in eyes	<ul style="list-style-type: none">• Hold eye open and rinse slowly and gently with water for 15-20 minutes.• Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.• Call a poison control center or doctor for treatment advice.
If on skin or clothing	<ul style="list-style-type: none">• Take off contaminated clothing.• Rinse skin immediately with plenty of water for 15-20 minutes.• Call a poison control center or doctor for treatment advice.

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS. CAUTION

Harmful if swallowed, inhaled or absorbed through skin. Causes moderate eye irritation. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Avoid breathing vapor. Avoid contact with eyes, skin or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before use.

HAZARDS TO DOMESTIC ANIMALS

For external use only. For use on dogs only. Do not use on cats or any animals other than dogs. Do not use on puppies under eight weeks of age. Consult a veterinarian before using this product on aged, debilitated, medicated, pregnant or nursing animals. Individual sensitivities while rare may occur after the use of any pesticide product. If signs persist or become more severe, consult a veterinarian immediately. For further product information call 1-800-477-1365.

PHYSICAL AND CHEMICAL HAZARDS

Combustible. Do not use or store near heat or open flame.

LIMITED WARRANTY AND DISCLAIMER

Recommendations for use of this product are based upon tests believed to be reliable. The use of this product being beyond control of the seller, no guarantee, express or implied, is made as to the effects of such use or the results to be obtained if not used in accordance with printed directions and established safe practice. Buyer's exclusive remedy and seller's exclusive liability for any and all claims, losses, damages or injuries resulting from the use or handling of this product, whether or not based in contract, negligence, strict liability in tort or otherwise shall be limited, at the seller's option to replacement of, or the repayment of the purchase price for, the quantity of product with respect to which damages are claimed.

**EPA Reg. No. 80490-
EPA Est. No.**

Manufactured For:
Fort Dodge Animal Health
P.O. Box 5366
Princeton, NJ 08543-5366

[CARTON LANGUAGE – FRONT PANEL]

Promeris Spot On for Dogs

SINGLE SPOT APPLICATION FOR CONTROL OF FLEAS AND TICKS ON DOGS AND PUPPIES OVER EIGHT WEEKS OF AGE.

For Dogs XX-XX lbs.

ACTIVE INGREDIENTS:

Metaflumizone (CAS No. 35037-73-1)	14.34%
Amitraz (CAS No. 33089-61-1)	14.34%
OTHER INGREDIENTS	<u>71.32%</u>
TOTAL.....	100.00%

Contains 6 – XX fl oz (XX mL) applicators

**KEEP OUT OF REACH OF CHILDREN
CAUTION**

For first aid and additional precautionary statements, refer to product package insert.

[Note: Five different packages (0.67, 1.33, 3.33, 5.33 and 6.66 mL/applicator) are available for various sizes of dogs. The XX lb dog body weight, XX fl oz and XX mL will be printed on the carton for each appropriate packaging size.]

[CARTON LANGUAGE - BACK PANEL]

Promeris Spot On for Dogs

Promeris Spot On for Dogs is a convenient single spot application, provides rapid control of existing flea and tick infestations and protects against reinfestation.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling. See inside pamphlet for additional directions for use. Read the entire label and enclosed directions before using the product. For use on dogs only.

For control of fleas and ticks, apply the contents of the applicator tube to a single spot on the skin of the dog between the shoulder blades. Remove the applicator tube from the package and holding the tube upright, bend the tip of the tube to break the tip along the fracture line. The top of the tip will fold back against the tube. Push the tip of the applicator tube through the dog's hair to the skin surface and squeeze the tube to expel the entire contents. Do not apply the product to the surface of the dog's coat. Monthly application is recommended to provide continuous effective control of fleas and ticks and prevent reinfestation.

EPA Reg. No. 80490-
EPA Est. No. XXX

Manufactured For:
Fort Dodge Animal Health
P.O. Box 5366
Princeton, NJ 08543-5366

Net Contents:

[FOIL CONTAINER LABEL LANGUAGE]

Promeris Spot On for Dogs

(14.34% Metaflumizone & 14.34% Amitraz)

**FOR DOGS AND PUPPIES OVER EIGHT WEEKS OF AGE.
For Dogs XX-XX lbs.**

**KEEP OUT OF REACH OF CHILDREN.
CAUTION**

How to apply: See "DIRECTIONS FOR USE" in the product package insert.

EPA Reg. No. 80490-
EPA Est. No. XXX
Lot No.

Contains XX fl oz (XX mL)

[APPLICATOR LABEL LANGUAGE]

**Promeris Spot On for Dogs
(14.34% Metaflumizone & 14.34% Amitraz)**

FOR DOGS AND PUPPIES OVER EIGHT WEEKS OF AGE.

For Dogs XX-XX lbs.

KEEP OUT OF REACH OF CHILDREN.

CAUTION

See product package insert for additional directions.

EPA Reg. No. 80490-

EPA Est. No. XXX-

Lot No.

Contains XX fl oz (XX mL)