Approval Date: June 4, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-915

B. Sponsor

Novartis Animal Health US, Inc.
Post Office Box 26402
Greensboro, NC 27404-6402

C. Proprietary Name

Safeheart™

D. Established Name

Milbemycin Oxime Tablets

E. Dosage Form

Oral Tablets

F. Route of Administration

SAFEHEART™ Tablets should be given by direct oral dosing.

G. Recommended Dose

SAFEHEART™ Tablets are given orally, once a month, at the recommended minimum dosage of 0.1 mg milbemycin oxime per kg of body weight (0.05 mg/lb).

Recommended Dosage Schedule

Body Weight	Tablet Size
2 - 50 lbs.	One Tablet (2.3 mg)
50.1 - 125 lbs.	One Tablet (5.75 mg)

NOTE: Dogs over 125 lbs. are provided the appropriate combination of tablets.

H. Indication

SAFEHEART™ Tablets are indicated for use in the prevention of heartworm disease in dogs and puppies four weeks of age or greater and two pounds body weight or greater.

I. Effect of Supplement

For the prevention of heartworm disease caused by *Dirofilaria immitis* in dogs and puppies four weeks of age or greater and 2 pounds of body weight or greater.

II. EFFECTIVENESS

Milbemycin oxime is an anthelmintic compound which, when given orally to animals, is effective in eliminating the tissue stage of heartworm larvae. The anthelmintic activity is believed to be a result of interference with invertebrate neurotransmission.

A. Dose Establishment Studies

Dose establishment studies in support of this product are referenced in the Freedom of Information (FOI) Summary for the original NADA 140-915 approval.

B. Well-Controlled Clinical Field Trial

Study No. CAH-4303-95-0096

Purpose: To evaluate the efficacy of milbemycin oxime when administered monthly at a minimum of 0.1 mg/kg by the pet owner for heartworm prevention.

Investigators/Study Locations:

Dr. William Craig
Ingram Park Animal Hospital
San Antonio, TX

Dr. Karen Kennedy
Guilford-Jamestown
Veterinary Hospital
Greensboro, NC

Dr. Dan J. McIlhany
Towne North Animal Hospital
San Antonio, TX

Type of Study: Clinical trial in client-owned dogs.

Animals: One hundred thirty-four (134) of the 150 client-owned dogs enrolled completed the 12 month study. Sixty-six (66) of the dogs that completed the study were in the low dose treatment group and sixty-eight (68) were in the positive control group.

Dosage Form: SAFEHEART™ Tablets

Route of Administration: Oral

Dose Tested: Minimum dose of 0.1 mg/kg

Frequency of Treatment: Monthly for 12 months. All dogs were tested for D. immitis microfilaria and antigen at months 5 and 12.

Control: Interceptorâ (milbemycin oxime) Flavor Tabs (minimum dose of 0.5 mg/kg)

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Duration of Study: Twelve months

Results: All dogs from both treatment groups were negative for D. immitis microfilaria and adult antigen at months 5 and 12.

Conclusions: The low dose of milbemycin oxime (0.1 mg/kg) provides effective heartworm prevention in the dog.

Adverse Reactions: The following clinical observations were noted during the study

	Number of Enrolled Dogs	
Observations	**SafeheartTM (n = 75)**	**Interceptorâ (n = 75)**
Anorexia/appetite	4	0
Vomiting	3	3
Diarrhea	3	1
Lethargy	2	1

III. ANIMAL SAFETY

Target animal safety studies in support of this supplement are referenced in the FOI Summary for the original NADA 140-915 approval.

IV. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food were not required for approval of this supplemental NADA. This drug is to be labeled for use in dogs which are non-food animals.

V. AGENCY CONCLUSIONS

The data in support of this supplement comply with the requirements of Section 512 of the Act and Part 514 of the implementing regulations. The data demonstrate that SAFEHEART™ (milbemycin oxime) Tablets, when used under labeled conditions of use, are safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106) this is a Category II change. This supplement provides for a change in dose for dogs from a minimum of 0.5 mg/kg to a minimum of 0.1 mg/kg with a corresponding restriction in indications to the prevention of heartworm disease only.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical for the diagnosis of heartworms and for the safe use of the product.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new dose and restricted indication for which the supplemental application was approved.

Patent # 4,547,520 expires on June 14, 2004

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.