Approval Date: April 10, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-084

B. Sponsor

Novartis Animal Health US, Inc.
Post Office Box 18300
Greensboro, NC 27419-8300

C. Proprietary Name

Sentinel™ Tablets

D. Established Name

milbemycin oxime/lufenuron tablets

E. Dosage Form, Route of Administration and Recommended Dosage

SENTINEL Tablets are given orally, once a month, at the recommended minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin and 4.55 mg/lb (10 mg/kg) lufenuron.

Recommended Dosage Schedule

Body Weight	Milbemycin Oxime per Tablet	Lufenuron per Tablet
2 to 10 lbs.	2.3 mg	46 mg
11-25 lbs.	5.75 mg	115 mg
26-50 lbs.	11.5 mg	230 mg
51-100 lbs.	23.0 mg	460 mg

Dogs over 100 lbs. are provided the appropriate combination of tablets.

F. Dispensing Status

Rx: U.S. Federal law restricts this drug to use by or on the order of a licensed veterinarian

G. Indication

SENTINEL Tablets are indicated for use in dogs and puppies four weeks of age and older and two pounds body weight or greater, for the prevention of heartworm disease caused by *Dirofilaria immitis*, for the prevention and control of flea populations, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara cani*s, Toxascaris leonina (roundworm) and *Trichuris vulpis* (whipworm) infections.

II. EFFECTIVENESS

The effectiveness of SENTINEL Tablets is based upon existing Novartis product approvals for milbemycin oxime (Interceptor Tablets, NADA 140-915) and lufenuron (Program Tablets, NADA 141-035).

Interceptor Tablets containing milbemycin oxime are approved for the prevention of heartworm disease caused by *Dirofilaria immitis*, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis*, *Toxascaris leonina* (roundworm) and *Trichuris vulpis* (whipworm) infections in dogs. Program Tablets containing lufenuron are approved for use in dogs, for the prevention and control of flea populations.

Well-controlled studies demonstrated that SENTINEL was equivalent to Interceptor Tablets and Program Tablets against the labeled parasites. The SENTINEL dosage, route of administration (oral), active ingredients and claims are identical to those approved for Interceptor and Program.

A. Nematode Efficacy Studies

Thirteen studies were conducted in dogs to demonstrate the efficacy of milbemycin oxime against nematodes. See the Interceptor tablet Freedom of Information (FOI) summaries for more information (NADA 140-915).

B. Flea Efficacy Studies

Four efficacy studies were conducted in dogs to demonstrate the efficacy of lufenuron against fleas. See the Program tablet FOI summary for more information (NADA 141-035).

C. Component Efficacy Studies - SENTINEL Tablets

Five studies were conducted to confirm the dose and demonstrate component efficacy for both milbemycin oxime and lufenuron in a combination tablet. One study each was conducted to confirm efficacy against heartworm (*Dirofilaria immitis*), fleas (*C. felis*), roundworm (*Toxocara canis*), hookworm (*Ancylostoma caninum*), and whipworm (*Trichuris vulpis*). All studies were conducted in a double-blind manner using the proposed final market formulation.

1. *Heartworm Efficacy Study*

   (i) Purpose: SENTINEL tablets, Interceptor tablets and Program tablets were compared for efficacy against heartworms (*Dirofilaria immitis*).

   (ii) Investigator: Byron Blagburn, Ph.D.

   (iii) Study Location:

   Auburn University
   Auburn, Alabama

   (iv) Type of Study: Experimental infection with L3 larvae of *Dirofilaria immitis*.

   (v) Animals: Forty Beagle dogs (20 males, 20 females, 1-4 years old) were divided into four groups of ten dogs each.

(vi) Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: Program (lufenuron) Tablets
- Group 3: Interceptor (milbemycin oxime) Tablets
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets

(vii) Route of Administration: Oral

(viii) Dose Tested:

- Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg

(ix) Frequency of Treatment: One dose at 1, 2, 3, 4 and 5 months after infection.

(x) Controls: Placebo control (group 1)

(xi) Duration of Study: Dogs experimentally infected with L3 larvae of *Dirofilaria immitis*. All dogs were euthanized and adult heartworms were counted six months post infection.

(xii) Results: Efficacy was calculated by comparing the number of adult heartworms in each of the treatment groups to the number of adult heartworms found in the control group.

The following table shows the percent efficacy for each treatment group.

Treatment	**Geometric Mean**	**% Efficacy**
Placebo	1.39 ± 1.28	---
Lufenuron	1.40 ± .102	-0.72%
Milbemycin Oxime	0.0 ± 0.0	100%
Combination	***0.0 ± 0.0***	100%

No worms were recovered from the group which received milbemycin oxime, or the milbemycin oxime/lufenuron combination tablet; this represents 100% prevention of *D. immitis*.

(xiii) Conclusions: SENTINEL was better than the placebo and the lufenuron treatment groups. SENTINEL was similar to the milbemycin treatment group, indicating that lufenuron did not interfere with the activity of milbemycin when administered in combination.

(xiv) Adverse Reactions: None reported.

2. *Flea Efficacy Study*

(i) Purpose: SENTINEL tablets, Interceptor tablets and Program tablets were compared for efficacy against fleas.

(ii) Investigator: Byron Blagburn, Ph.D.

(iii) Study Location:

Auburn University
Auburn, Alabama

(iv) Type of Study: Periodic infestation with newly emerged fleas throughout the study.

(v) Animals: Forty Beagle dogs (20 males, 20 females, 4-5 years old) were divided into four groups of ten dogs each.

(vi) Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: Program (lufenuron) Tablets
- Group 3: Interceptor (milbemycin oxime) Tablets
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets

(vii) Route of Administration: Oral

(viii) Dose Tested:

- Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg

(ix) Frequency of Treatment: One treatment on day 16 or 17 of the study.

(x) Controls: Placebo control (group 1)

(xi) Duration of Study: All dogs were infested with newly emerged adult fleas 2-3 times per week for 7 weeks and flea eggs were collected once weekly, placed in flea rearing medium and allowed to emerge.

(xii) Results: Efficacy was calculated by comparing the development of eggs collected from fleas feeding on each of the three treated groups versus control animals. The following table shows the cumulative developmental success rates between days 7 and 33 post-treatment (efficacy was based on the first month only based on the monthly dosing interval).

Treatment Group	**No. Fleas/No.Eggs Collected**	**Emergence Rate**
Placebo	1535 / 2500	61.4%
Lufenuron	178 / 2357	7.6%
Milbemycin	1328 / 2220	59.8%
Milbemycin/Lufenuron	171 / 2418	7.1%

Lufenuron tablets and milbemycin oxime/lufenuron combination tablets reduced flea emergence by 88.1 and 87.8%, respectively.

Because fleas were recovered from dogs in each treatment group, treatment comparisons were made using logistic regression techniques and assuming a model containing treatment effects only. The Wald X^2 test statistic was used to test for treatment differences using pairwise comparisons of treatment groups.

Treatment Comparisons	**Prob. >x**
Milbemycin/Lufenuron vs Placebo	.0001
Milbemycin/Lufenuron vs Lufenuron	.5241
Milbemycin/Lufenuron vs Milbemycin	.0001

(xiii) Conclusions: SENTINEL was better than the placebo (p = .0001) and the milbemycin (p = .0001) treatment groups. The combination was similar to the lufenuron treatment group (p = .5241) indicating that milbemycin did not interfere with the activity of lufenuron when administered in combination.

(xiv) Adverse Reactions: None reported.

3. *Roundworm Efficacy Study*

(i) Purpose: SENTINEL tablets, Interceptor tablets and Program tablets were compared for efficacy against roundworms *(Toxocara canis*).

(ii) Investigator: Dwight Bowman, Ph.D.

(iii) Study Location:

CHK - R&D
Stanwood, Michigan

(iv) Type of Study: Natural infections of roundworms (*Toxocara canis*).

(v) Animals: Forty adult dogs (22 male, 18 female) of various breeds were divided into four groups of ten dogs each.

(vi) Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: Program (lufenuron) Tablets
- Group 3: Interceptor (milbemycin oxime) Tablets
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets

(vii) Route of Administration: Oral

(viii) Dose Tested:

- Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg

(ix) Frequency of Treatment: One treatment.

(x) Controls: Placebo control (group 1)

(xi) Duration of Study: The dogs were euthanized 7 days after treatment and adult worms were recovered, identified and counted.

(xii) Results: Efficacy was calculated by comparing the number of worms collected from each of the treatment groups versus control animals. The following table shows the percent efficacy for each group.

Treatment	**Geometric Mean**	**% Efficacy**
Placebo	1.098 ± .510	---
Lufenuron	.816 ± .508	25.7%
Milbemycin Oxime	.030 ± .095	97.3%
Combination	.060 ± .127	94.5%

Because worms were recovered from dogs in each treatment group, counts were logarithmically transformed and analysis of variance was done for the treatment comparisons of interest.

Treatment Comparisons	**Two-sides p-values**
Milbemycin/Lufenuron vs Placebo	.0001
Milbemycin/Lufenuron vs Lufenuron	.0001
Milbemycin/Lufenuron vs Milbemycin	.8561

(xiii) Conclusions: SENTINEL was better than the placebo (p = .0001) and the lufenuron (p = .0001) treatment groups. The combination was similar to the milbemycin treatment group (p = .8561), indicating that lufenuron did not interfere with the activity of milbemycin when administered in combination.

(xiv) Adverse Reactions: None reported.

4. *Hookworm Efficacy Study*

(i) Purpose: SENTINEL tablets, Interceptor tablets and Program tablets were compared for efficacy against hookworms (*Ancylostoma caninum*).

(ii) Investigator: Dwight Bowman, Ph.D.

(iii) Study Location:

CHK - R&D
Stanwood, Michigan

(iv) Type of Study: Natural infections of hookworms (*Ancylostoma caninum*).

(v) Animals: Forty adult dogs (20 males, 20 females) of various breeds were divided into four groups of ten dogs each.

(vi) Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: Program (lufenuron) Tablets
- Group 3: Interceptor (milbemycin oxime) Tablets
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets

(vii) Route of Administration: Oral

(viii) Dose Tested:

- Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg

(ix) Frequency of Treatment: One treatment.

(x) Controls: Placebo control (group 1)

(xi) Duration of Study: The dogs were euthanized 7 days after treatment and adult worms were recovered, identified and counted.

(xii) Results: Efficacy was calculated by comparing the number of worms recovered from each of the three treatment groups versus control animals. The following table shows the percent removal for each group.

Treatment	**Geometric Mean**	**% Efficacy**
Placebo	1.426 ± .619	---
Lufenuron	1.099 ± .523	22.9%
Milbemycin Oxime	0.030 ± .095	97.9%
Combination	.301 ± .763	78.9%*

* One dog harbored 253 worms at necropsy. A total of 3 worms were recovered from the remaining 9 dogs in this group.

Because worms were recovered from dogs in each treatment group, counts were logarithmically transformed and analysis of variance was done for the comparisons of interest.

Treatment Comparisons	**Two-sides p-values**
Milbemycin/Lufenuron vs Placebo	.0001
Milbemycin/Lufenuron vs Lufenuron	.0029
Milbemycin/Lufenuron vs Milbemycin	.2862

(xiii) Conclusions: SENTINEL was better than the placebo (p = .0001) and was better than the lufenuron (p = .0029) treatment groups. The combination was similar to the milbemycin treatment group (p = .2862), indicating that lufenuron did not interfere with the activity of milbemycin when administered in combination.

(xiv) Adverse Reactions: None reported.

5. *Whipworm Efficacy Study*

(i) Purpose: SENTINEL tablets, Interceptor tablets and Program tablets were compared for efficacy against whipworms (*Trichuris vulpis*).

(ii) Investigator: Dwight Bowman, Ph.D.

(iii) Study Location:

CHK - R&D
Stanwood, Michigan

(iv) Type of Study: Natural infections of whipworms (*Trichuris vulpis*).

(v) Animals: Forty adult dogs (18 males, 22 females) were divided into four groups of ten dogs each.

(vi) Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: Program (lufenuron) Tablet
- Group 3: Interceptor (milbemycin oxime) Tablets
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets

(vii) Route of Administration: Oral

(viii) Dose Tested:

- Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg

(ix) Frequency of Treatment: One treatment.

(x) Controls: Placebo control (group 1)

(xi) Duration of Study: The dogs were euthanized 7 days after treatment and adult worms were recovered, identified and counted.

(xii) Results: Efficacy was calculated by comparing the number of worms recovered from each of the three treatment groups versus control animals. The following table shows the percent removal for each group.

Treatment	**Geometric Mean**	**% Efficacy**
Placebo	1.905 ± .701	---
Lufenuron	1.831 ± .678	3.9%
Milbemycin Oxime	.770 ± 1.36	59.6%
Combination	.770 ± 1.36	90.4%*

* One dog harbored 247 worms at necropsy. A total of 7 worms were recovered from the remaining 9 dogs in the group.

Because worms were recovered from dogs in each treatment group, counts were logarithmically transformed and analysis of variance was done for the comparisons of interest.

Treatment Comparisons	**Two-sides p-values**
Milbemycin/Lufenuron vs Placebo	.0001
Milbemycin/Lufenuron vs Lufenuron	.0001
Milbemycin/Lufenuron vs Milbemycin	.5178

(xiii) Conclusions: SENTINEL was better than the placebo (p = .0001) and was better than the lufenuron (p = .0001) treatment groups. The combination was similar to the milbemycin treatment group (p = .5178), indicating that lufenuron did not interfere with the activity of milbemycin when administered in combination.

(xiv) Adverse Reactions: None reported.

D. Clinical Trials - SENTINEL Tablets

Two clinical field trials were conducted to supplement data obtained in the original clinical trials conducted under NADA 140-915 and NADA 141-035. The General Clinical Trial demonstrated efficacy against four target parasites; fleas, roundworms, hookworms and whipworms. The Roundworm Clinical Trial generated additional information on roundworm efficacy.

1. *General Clinical Trial*

   (i) Purpose: To evaluate SENTINEL tablets in clinical use.

   (ii) Investigators/Study Locations:

Mildred Bass, DVM
Village Veterinary Clinic
12249 Kingston Pike
Farragut, TN 37922

Alan Bater, MRCVS
Freeport Animal Clinic
P.O. Box F-724
Freeport, Grand Bahamas

Mark Epstein, DVM (Site 3)
Paw Creek Animal Hospital
11226 Mount Holly Road
Charlotte, NC 28214

Mark Epstein, DVM (Site 4)
Bethel Animal Hospital
125 Forest Oaks Drive
Lake Wylie, SC 29710

Jim Raab, DVM
Tri-County Animal Hospital
1807 Okeechobee Road
Fort Pierce, FL 34950

Denis Scarpinato, DVM
Pinewoods Animal Hospital
1905 43rd
Vero Beach, FL 32960

Gary Brotze, DVM
Creekview Veterinary Clinic
1121 Eikel
New Braunfels, TX 78130

Jay Butan, DVM
Canal Animal Hospital
501 24th Avenue, North
Lake Worth, FL 33460

Jerry Greene, DVM
Academe Animal Hospital
912 East Fletcher Avenue
Tampa, FL 33612

Joe Kinnarney, DVM
Reidsville Veterinary Hospital
1401 West Harrison St.
Reidsville, NC 27320

Scott Siegel, DVM
Logan Animal Hospital
103 Justice Avenue
Logan, WV 25601

Jan Strother, DVM
No. Alabama Cat & Bird
Veterinary Clinic
Route 4, Box 92
Hartselle, AL 35640

Bill Campaigne, DVM
Seguin Animal Hospital
1252 West Kingsbury
Seguin, TX 78155

John Lewis, DVM
Madison Veterinary Clinic
1309 West Base St.
Madison, FL 32340

Gary Wilson, DVM
Animal Hospital of New Caney
Route 2, Box 1060
New Caney, TX 77357

Mark Epstein, DVM (Site 2)
New Hope Animal Hospital
3435 South New Hope Rd.
Gastonia, NC 28056

Mark Epstein, DVM (Site 1)
Forestbrook Animal Hospital
3200 Union Road
Gastonia, NC 38056

Ann Parker, DVM
Hope Mills Road Animal Hospital
2301 Hope Mills Road
Fayetteville, NC 28304

Karen Wylie, DVM
Leland Animal Clinic
302 Bankhead Highway
Mableton, GA 30059

(iii) Type of Study: Natural infections (fleas, roundworms, hookworms and whipworms) in pet dogs.

(iv) Animals: Two hundred sixty-nine (269) client owned dogs were enrolled in the study and two hundred forty-seven (247) were included in the final efficacy analysis.

(v) Dosage Form: SENTINEL (Milbemycin Oxime/Lufenuron) Tablets

(vi) Route of Administration: Oral

(vii) Dose Tested:

- Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg

(viii) Frequency of Treatment: Six monthly doses.

(ix) Controls: None

(x) Duration of Study: Each dog was dosed monthly with the test drug for six months. Each dog was evaluated every month by the clinical investigator. Flea counts were performed every month. Testing for heartworms by occult testing and microfilariae examination was done on all dogs over 6 months of age; at enrollment, at month three and at month six of the study. Fecal flotation for gastrointestinal parasites was performed at enrollment, at month 1, 2 and 3 and at follow-up examinations 7-18 days after any positive fecal.

(xi) Results: Efficacy was evaluated against roundworm, hookworm, and whipworm after 3 months. Efficacy against fleas was evaluated after 6 months of administration. The results are displayed in the following table.

Parasite	**Treatment/Reduction % (number of dogs)**	**Control % (number of dogs)**
Roundworm	96.5% (57)	100.0% (38)
Hookworm	---	87.3% (103)
Whipworm	89.3% (56)	93.0% (43)
Flea Count Reduction[1]	82.5% (161)	---
Dogs With Adequate Flea Control[2]	---	85.7% (161)

Flea reduction evaluated in dogs kept in controlled environments only; i.e., dogs that had frequent contact with untreated animals and/or untreated environments were excluded from analysis.

The majority (>82%) of dogs showed adequate control of flea populations with with flea counts of five or fewer at months four, five and six. Due to the length of the trial (6 months) and the prepatent period of the heartworm (approximately 6.5 months), the efficacy of the drug for the prevention of heartworms could not be scientifically evaluated.

(xii) Conclusions: SENTINEL tablets provided adequate efficacy against the target parasites.

(xiii) Adverse Reactions: The following clinical observations were noted during the 6 month study.

Observation	**Number of Dogs**	**Percent of Dogs (n=269)**
Diarrhea	8	3.0%
Vomiting	6	2.2%
Anorexia	4	1.5%

2. *Roundworm Clinical Trial*

(i) Purpose: To evaluate SENTINEL tablets in clinical use against roundworms.

(ii) Investigators/Study Locations:

Mildred Bass, DVM
Village Veterinary Clinic
12249 Kingston Pike
Farragut, TN 37922

Alan Bater, MRCVS
Freeport Animal Clinic
P.O. Box F-724
Freeport, Grand Bahamas

Dennis Scarpinato, DVM
Pinewoods Animal Hospital
1905 43rd
Vero Beach, FL 32960

Scott Siegel, DVM
Logan Animal Hospital
103 Justice Avenue
Logan, WV 25601

Gary Wilson, DVM
Animal Hospital of New Caney
Route 2, Box 1060
New Caney, TX 77357

Karen Wylie, DVM
Leland Animal Clinic
302 Bankhead Highway
Mableton, GA 30059

Ann Parker, DVM
Hope Mills Road Animal Hospital
2307 Hope Mills Road
Fayetteville, NC 28304

(iii) Type of Study: Natural infections by roundworms in pet dogs.

(iv) Animals: Fifty seven (57) client owned dogs were enrolled in the study. Thirty-eight (38) were placed in the SENTINEL treatment group and nineteen (19) placed in the pyrantel pamoate group.

(v) Dosage Form:

- SENTINEL (Milbemycin Oxime/Lufenuron) Tablets
- Pyrantel Pamoate

(vi) Route of Administration: Oral

(vii) Dose Tested:

- SENTINEL (Milbemycin Oxime 0.5 mg/kg/Lufenuron 10 mg/kg)
- Pyrantel Pamoate (labeled dose)

(viii) Frequency of Treatment: One or two monthly doses.

(ix) Controls: Pyrantel Pamoate

(x) Duration of Study: Each dog had roundworms at the start of the trial, and was given the test drug or pyrantel pamoate. A fecal examination was performed 7-18 days later. The dogs returned one month after the first dose and were checked again for roundworms. If positive, they were dosed again and checked 7-18 days later, if negative, they were finished at the month one examination. All remaining dogs were finished at the month one follow-up fecal.

(xi) Results: Efficacy was evaluated against roundworms and is displayed in the following table.

Test Article	**Removal Claim**	**Control Claim**
Combination	97.5%	85.7%
Pyrantel Pamoate	76.5%	84.6%

(xii) Conclusions: Based on an odds ratio test, SENTINEL was no worse than the positive control in the removal and control of roundworms.

(xiii) Adverse Reactions: The following clinical observations were noted during study.

Number and Percent of Dogs

Observation	**Combination (n = 38)**	**Pyrantel Pamote (n = 19)**
Diarrhea	1 (2.6%)	1 (5.3%)
Vomiting	3 (7.9%)	0 (0.0%)

III. TARGET ANIMAL SAFETY

A. Milbemycin Oxime Safety Studies

Six target animal safety studies were conducted in dogs to address the safety of milbemycin oxime. See the Interceptor Tablet FOI Summaries for more information.

B. Lufenuron Safety Studies

Nine target animal safety studies were conducted in dogs to address the safety of lufenuron. See the Program Tablet FOI Summary for more information.

C. SENTINEL Safety Studies

Three target animal safety studies were conducted in dogs to address the safety of the milbemycin oxime/lufenuron combination drug.

1. *Acute Oral Toxicity Study in Dogs with Milbemycin Oxime/Lufenuron Combination Tablet*

   (i) Purpose: To evaluate the safety of SENTINEL (milbemycin oxime/lufenuron) tablets when given at 10X the projected use rate.

   (ii) Investigator: Dennis J. Naas, BS

   (iii) Study Location:

   Wil Research Laboratories
   Ashland, Ohio

   (iv) Type of Study: Laboratory safety study

   (v) Animals: Twelve Beagle dogs (6 males, 6 females, 15-24 months of age)

   (vi) Dosage Forms:

   - Group 1: Placebo Tablets (vehicle)
   - Group 2: SENTINEL Tablets

(vii) Route of Administration: Oral

(viii) Dose Tested:

- Milbemycin Oxime 5.0 mg/kg (10X the monthly use rate)
- Lufenuron 100 mg/kg (10X the monthly use rate)

(ix) Frequency of Treatment: One dose.

(x) Controls:

- Group 1: Placebo control group.

(xi) Duration of Study: The animals were observed twice daily for signs of mortality and morbidity. The animals were also observed for clinical signs at the time of dosing and at 1, 2, 4, 8, 12 and 24 hours following dosing. Animals were also observed daily for a two-week observation period following dosing.

Veterinary examinations were conducted prior to the initiation of dosing and prior to necropsy. Individual body weights were recorded weekly. Food consumption was recorded daily and reported weekly. Clinical pathology evaluations (hematology, serum chemistry and urinalysis) were performed on week -1 (pretest), 0 and 2. Complete necropsies were performed on each dog.

(xii) Results: All animals survived to the scheduled necropsy. The following clinical observations were recorded during the study: vomiting-- 3 dogs in the placebo group at 4, 11, and 13 days post treatment and 4 dogs in the combination group at 1, (2 and 12)[1], 4 and 12 days post treatment; salivation--1 dog in the combination group at 0, 1 and 2 hours post treatment.

Mean body weights, body weight changes and food consumption were unaffected by treatment. No clinically significant changes were apparent in the hematology, serum chemistry and urinalysis parameters. Macroscopic findings were unaffected by treatment.

(xiii) Conclusions: Milbemycin oxime/lufenuron combination tablets are safe when administered orally to beagle dogs at dose levels of 5 mg/kg milbemycin oxime and 100 mg/kg lufenuron (10X the month ad usum level). Vomiting was observed in 3 placebo (vehicle)-treated dogs and in 4 combination-treated dogs. Salivation was noted in 1 dog treated with the combination drug for up to 2 hours post treatment.

2. *A 2-Month Oral Toxicity Study of Milbemycin Oxime/Lufenuron Tablets in Beagle Puppies, Starting at Two Weeks of Age*

(i) Purpose: To evaluate the safety of SENTINEL (milbemycin oxime/lufenuron) tablets when given at up to 5X the projected use rate to puppies.

(ii) Investigator: Dennis J. Naas, BS

[1] One dog vomited twice, at day 2 and day 12.

(iii) Study Location:

Wil Research Laboratories
Ashland, Ohio

(iv) Type of Study: Laboratory safety study

(v) Animals: Forty-eight (24 males, 24 females) 2-week old Beagle puppies were divided into four groups of six males and six females. The puppies remained with the lactating bitches until weaning was completed.

(vi) Dosage Forms:

- Group 1: Placebo Tablets (vehicle)
- Group 2: SENTINEL (milbemycin oxime/lufenuron) Tablets at 1X
- Group 3: SENTINEL (milbemycin oxime/lufenuron) Tablets at 3X
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets at 5X

(vii) Route of Administration: Oral

(viii) Dose Tested:

- 1X - Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg
- 3X - Milbemycin Oxime 1.5 mg/kg
- Lufenuron 30 mg/kg
- 5X - Milbemycin Oxime 2.5 mg/kg
- Lufenuron 50 mg/kg

(ix) Frequency of Treatment: Single doses on days 0, 14, 28, 42 and 56.

(x) Controls: Group 1: Placebo (vehicle) control group.

(xi) Duration of Study: All puppies were observed twice daily for signs of morbidity and mortality until one week after the last dose. Observations included clinical signs, (twice daily and hourly for 8 hours on the days of dosing), body weight (twice weekly), hematology, serum chemistry, ophthalmic exams (weeks 4 and 8), gross pathology and organ weights.

(xii) Results: Four deaths occurred (two females in the control, one male in the 1X and one male in the 5X groups); the deaths were not attributed to the test drug.

CNS/behavior findings occurred in the 3X and 5X groups early in the study period (when puppies were 2-4 weeks of age). These findings consisted predominantly of incoordination, generalized tremors and unable to be aroused. These clinical signs were limited to pups in the 5X dose group following the first and/or second dosing (study days 0 and 14, respectively) and pups in the 3X dose group following the first dose only. In some cases the CNS/behavior findings persisted for one or two days following test article administration. All affected animals showed full recovery. Tail twitching was observed for one male in the 5X group after the first dose, persisting for 3 days. None of the aforementioned signs were observed after the third, fourth and fifth dosings (study days 28, 42 and 56, respectively).

No adverse effects were observed on body weights, body weight gains or hematology and serum chemistry parameters. No adverse effects were observed at the ophthalmic and macroscopic examinations. Organ weights were unaffected by treatment.

(xiii) Conclusions: SENTINEL caused changes in CNS/behavior (incoordination, generalized tremors, inability to arouse and/or tail twitching) in 2-week-old puppies treated at 3X and 5X the recommended dose and in 4-week-old puppies treated at 5X the recommended dose

3. *A 6-Month Oral Toxicity Study of Milbemycin Oxime/Lufenuron Tablets (SENTINEL) in Young Beagle Dogs*

(i) Purpose: To evaluate the safety of SENTINEL (milbemycin oxime/lufenuron) tablets when given at doses up to 5X the projected use rate to dogs for six months.

(ii) Investigator: Dennis J. Naas, BS

(iii) Study Location:

Wil Research Laboratories
Ashland, Ohio

(iv) Type of Study: Laboratory safety study

(v) Animals: Forty-eight (24 males, 24 females) 2 month old Beagle puppies were divided into four groups of six males and six females.

(vi) Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: SENTINEL (milbemycin oxime/lufenuron) Tablets at 1X
- Group 3: SENTINEL (milbemycin oxime/lufenuron) Tablets at 3X
- Group 4: SENTINEL (milbemycin oxime/lufenuron) Tablets at 5X

(vii) Route of Administration: Oral

(viii) Dose Tested:

- 1X - Milbemycin Oxime 0.5 mg/kg
- Lufenuron 10 mg/kg
- 3X - Milbemycin Oxime 1.5 mg/kg
- Lufenuron 30 mg/kg
- 5X - Milbemycin Oxime 2.5 mg/kg
- Lufenuron 50 mg/kg

(ix) Frequency of Treatment: Single doses per day for three sequential days starting on days 0, 28, 53, 87, 112, 140, 171 and 200.

(x) Controls:

- Group 1: Placebo (vehicle) control group.

(xi) Duration of Study: All dogs were observed until 3 or 4 days after the last dose. Observations included clinical signs, body weight, food consumption, periodic hematology, serum chemistry, urinalysis, ophthalmic examinations as well as gross pathology, organ weight and histopathology.

(xii) Results: All animals survived to the scheduled necropsy at week 29. The following clinical observations are considered probably related to treatment with either the active combination tablet or the vehicle control tablet: Diarrhea/soft stools, vomiting, and red, raised skin lesions. Salivation was noted in 7 dogs (2 at 1X, 2 at 3X and 3 at 5X). Six of these 7 dogs salivated either at the time of dosing or within 1 hour after a treatment.

Mean body weight changes, food consumption and organ weights were unaffected by treatment. No abnormal changes were apparent when hematology, serum chemistry and urinalysis parameters were evaluated. Ophthalmic examinations revealed no adverse findings.

(xiii) Conclusions: SENTINEL is safe for use in dogs and puppies 2 months of age and older at doses up to 5X the recommended dose.

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this 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 NADA comply with the requirements of Section 512 of the Act and Section 514 of the Implementing regulations. The data demonstrate that SENTINEL Tablets (milbemycin oxime/lufenuron), when used under labeled conditions of use are safe and effective.

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, whipworms and hookworms and for the safe use of the product.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved and studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

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.