APPROVAL DATE: SEPTEMBER 27, 2002

FREEDOM OF INFORMATION SUMMARY

New Animal Drug Application
NADA 141-208

Advantage® DUO
(imidacloprid / ivermectin)
Topical Solution

Advantage® DUO is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. Advantage® DUO kills adult fleas and is indicated for the treatment of flea infestations *(Ctenocephalides felis)*.

Bayer Corporation
Agriculture Division
Animal Health

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Freedom of Information Summary

I. GENERAL INFORMATION

A.	File Number:	NADA 141-208
B.	Sponsor:	Bayer Corporation Agriculture Division Animal Health P. O. Box 390 Shawnee Mission, Kansas 66201 Drug Labeler Code: 000859
C.	Established Name:	Imidacloprid/Ivermectin
D.	Proprietary Name:	Advantage® DUO
E.	Dosage Form:	Colorless to yellow ready-to-use solution
F.	How Supplied:	Unit applicator tube Applicator Tube Size and Applications Per Package: 6 x 0.4 mL tubes 6 x 1.0 mL tubes 6 x 2.5 mL tubes 6 x 4.0 mL tubes
G.	How Dispensed:	Rx: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
H.	Amount of Active Ingredients:	100 mg Imidacloprid and 800 mcg Ivermectin/mL
I.	Route of Administration:	Topical
J.	Species/Class:	Canine
K.	Recommended Dosage	Recommended minimum dosage is 4.5 mg/lb (10 mg/kg) of imidacloprid + 36.4 mcg/lb (80 mcg/kg) of ivermectin once a month. Administer the entire contents of a unit applicator tube of Advantage DUO topically once a month as specified in the following table:

Dog (lb)	Advantage DUO	Volume (mL)	mg Imidacloprid	mcg Ivermectin
Up to 9	Advantage DUO 9	0.4	40	320
10.1 – 20	Advantage DUO 20	1.0	100	800
20.1-55	Advantage DUO 55	2.5	250	2000
55.1 - 88*	Advantage DUO 88	4.0	400	3200

*Dogs over 88 lbs should be treated with the appropriate combination of Advantage DUO tubes.

L. Pharmacological Category: Parasiticide

M. Indications: Advantage DUO is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. Advantage DUO kills adult fleas and is indicated for the treatment of flea infestations (*Ctenocephalides felis*).

II. EFFECTIVENESS

A. DOSAGE CHARACTERIZATION FOR FLEAS

Efficacy Evaluation of Imidacloprid 10% Solution Applied Dermally for Control of Fleas on Dogs. Report # 74572

Purpose: To evaluate initial and residual flea control effectiveness of three imidacloprid dose levels on dogs.

Investigator: Jerry Cunningham, M.S.

Study Director: Ronald Everett, Ph.D.

Study Location: AgResearch Consultants, Inc.
Greenbrier, AR

Animals: 32 dogs (18 females and 14 males), 2 to 9 years of age, 8 per group (Groups 1 and 2 had 4 females and 4 males; Groups 3 and 4 had 5 females and 3 males).

Dosage Groups: Group 1: 3.75 mg/kg imidacloprid
Group 2: 7.5 mg/kg imidacloprid
Group 3: 10.0 mg/kg imidacloprid
Group 4: Vehicle

Route of Administration: Topical, single spot between shoulder blades.

Frequency of Treatment: Once

Duration of Study: 34 days

Study Design: Each dog was infested with 100 unfed adult fleas on study days –1, 6, 13, 20, 27, and 33. Dogs were visually examined for fleas on days 1, 7, 14, 21, and 28. On day 34, the dogs were combed and fleas removed and counted. Dogs were observed 30 minutes, 1, 3, and 5 hours post-treatment and daily thereafter.

Results: Effectiveness of imidacloprid against adult fleas on dogs compared to the control is shown in the following table:

	Control	Group 1 (3.7 mg/kg)		Group 2 (7.5 mg/kg)		Group 3 (10 mg/kg)	
Day	Total Fleas	Total Fleas	% Effective	Total Fleas	% Effective	Total Fleas	% Effective
1	553	17	96.9%	12	97.8%	4	99.3%
7	751	7	99.1%	0	100%	0	100%
14	911	51	94.4%	9	99.0%	1	99.9%
21	953	30	96.8%	12	98.7%	0	100%
28	873	40	95.4%	14	98.4%	6	99.3%
34*	1171	98	91.6%	28	97.6%	36	96.9%

* Fleas were comb counted and removed.

Conclusions: Imidacloprid applied topically as a single dose of 3.75 mg/kg, 7.5 mg/kg or 10 mg/kg was effective against adult fleas. Effectiveness was 91.6%, 97.6% and 96.9% after receiving a single topical dose of imidacloprid at Day 34 for 3.7 mg/kg, 7.5 mg/kg, or 10 mg/kg respectively. The dosage of 10 mg/kg was selected for treatment of flea infestations in the dog.

Adverse Reactions: None reported.

B. DOSAGE CHARACTERIZATION FOR HEARTWORMS AND NON-INTERFERENCE STUDY AGAINST HEARTWORMS AND FLEAS

Efficacy of Imidacloprid + Ivermectin Applied Topically Against Developing Stages of Heartworm (*Dirofilaria immitis*) and Experimental Infestations of Fleas (*Ctenocephalides felis*) on Dogs. Report #75078

Purpose: The objectives were to a) confirm the dose of ivermectin applied topically against 30 day old heartworm infections, b) demonstrate that imidacloprid alone would not prevent heartworm infection, c) demonstrate that ivermectin is not efficacious against the flea and d) provide additional information on the effectiveness of imidacloprid against fleas.

Study Director: Dr. L. Cruthers

Study Location: PLRS
Corapeake, NC

Animals: 49 beagles (26 males and 23 females), 8 – 20 months old. Eight dogs per group except Group 1 had 9 dogs.

Dosage Groups: Group 1: 10 mg/kg imidacloprid + 40 mcg/kg ivermectin (0.1 mL/kg)
Group 2: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin (0.1 mL/kg)
Group 3: 10 mg/kg imidacloprid + 160 mcg/kg ivermectin (0.1 mL/kg)
Group 4: 10 mg/kg imidacloprid alone (0.1 mL/kg)
Group 5: 160 mcg/kg ivermectin alone (0.1 mL/kg)
Group 6: Vehicle

Route of Administration: Topical, at one site on the dorsal midline between the shoulder blades.

Frequency of Treatment: Once

Duration of Study: 153 days

Study Design: On Day –29 or –33, dogs were infected with approximately 50 infective (*D. immitis*) larvae harvested from mosquitoes. All dogs were tested for existing heartworm infections by both the modified Knott's test and the ELISA test prior to the start of the study and on Day 90. Dogs were infested with 100 unfed adult fleas (*Ctenocephalides felis*) on Day –3. A comb count was performed on Day –2 to establish pretreatment parasite burdens. On study days –1, 6, 13, 20, 27, 34, and 41 each dog was infested with approximately 100 unfed adult fleas. All dogs were individually housed during flea infestations and counts.

Parameters Measured: Flea comb counts were conducted on Days 1, 7, 14, 21, 28, and 35. Fleas were counted and removed. After treatment on Day 0, dogs were observed at 30 minutes, 1, 3 and 5 hours and then daily afterward. Effectiveness against flea infestations was calculated by comparing the geometric mean number of fleas on the control group with that of the treated groups. The dogs were euthanized and examined for adult heartworms on Days 150 or 153.

Results: Percent effectiveness of imidacloprid + ivermectin against adult fleas compared to controls and number of heartworms found at necropsy are shown in the table below. Geometric mean # of fleas is shown in parenthesis for the control animals.

	Percent Flea Effectiveness						# Heartworms
Group	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 150-153
1	100.0	99.9	99.2	95.6	82.0	38.2	0
2	99.5	99.6	100	93.6	78.0	52.3	0
3	100	100	99.7	96.6	69.1	37.3	0
4	100	100	99.4	95.7	83.0	58.2	74
5	8.9	18.6	-42.4	-28.4	14.0	2.6	0
6	(52.87)	(64.07)	(52.79)	(48.38)	(68.73)	(54.85)	67

Conclusion: Effectiveness of all three combination products (groups 1-3) and imidacloprid alone (group 4) against flea infestations was 93.6% to 100% up to Day 21. After Day 21, effectiveness decreased to below 90% for all groups. All three concentrations of ivermectin (40, 80, 160 mcg/kg) were 100% effective against the prevention of heartworm development. Ivermectin alone provided little to no flea

control and did not interfere with the activity of imidacloprid against fleas. Imidacloprid did not interfere with the activity of ivermectin against the prevention of heartworm development. The dosage of 80 mcg/kg ivermectin was chosen to be used in combination with imidacloprid for the prevention of heartworm disease in the dog.

Adverse Reactions: None reported.

C. EFFECTIVENESS STUDIES AGAINST FLEAS:

1. Efficacy of Topically Applied Imidacloprid + Ivermectin Against Flea (*Ctenocephalides felis*) Infestations on Dogs. Report #75108

Purpose: The objectives were to 1) determine the effectiveness of topically applied imidacloprid + ivermectin against flea infestations on dogs and 2) to demonstrate that ivermectin does not interfere with the insecticidal activity of imidacloprid against fleas.

Study Director: David R. Young, DVM, Ph.D.

Study Location: Young Veterinary Research Services
Turlock, CA

Animals: 24 dogs (12 males and 12 females), 21.8 – 77.8 lbs, 1 - 2 years old of various hair coat lengths. 8 dogs per group.

Dosage Groups: Group 1: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin
Group 2: 10 mg/kg imidacloprid alone
Group 3: Vehicle

Test Article Dosage:

≤ 10 lbs	0.4 mL
10.1 – 20 lbs	1.0 mL
20.1 – 55 lbs	2.5 mL
> 55 lbs	4.0 mL

Route of Administration: Topical, at one site on the dorsal midline between the shoulder blades.

Frequency of Treatment: Once

Duration of Study: 35 days

Study Design: All dogs were tested for existing heartworm infections by the ELISA test. Dogs were infested with 100 unfed adult fleas (*Ctenocephalides felis*) on Day –3. A comb count was performed on Day –2 to establish pretreatment parasite burdens. On Days –1, 6, 13, 20, 27, and 34 each dog was infested with approximately 100 unfed adult fleas.

Parameters Measured: Flea comb counts were conducted on Days 1, 7, 14, 21, 28, and 35. Fleas were counted and removed. Dogs were observed 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-treatment and twice daily thereafter. Effectiveness against flea infestations was calculated by comparing the geometric mean number of fleas on the control group with that of the treated groups.

Results: Percent effectiveness of imidacloprid + ivermectin against flea infestations is shown in the table below with the geometric mean # of fleas shown in parenthesis.

	Percent Flea Effectiveness (geometric mean # of fleas)		
Day	Group 1	Group 2	Group 3
1	99.8 (0.1)	99.8 (0.1)	(81.1)
7	100 (0)	99.9 (0.1)	(84.5)
14	99.8 (0.2)	100 (0)	(85.6)
21	99.5 (0.4)	100 (0)	(85.4)
28	96.5 (3.0)	95.1 (4.2)	(86.8)
35	96.7 (2.9)	99.2 (0.7)	(86.3)

Conclusion: Effectiveness of imidacloprid either alone or in combination with ivermectin against flea infestations was 95.1% to 100% up to Day 35. The combination product ivermectin + imidacloprid is as effective as imidacloprid alone against flea infestations. Ivermectin did not interfere with the activity of imidacloprid against fleas.

Adverse Reactions: One dog in Group 1 had spiking of the hair coat at the treatment site one day post-treatment which resolved spontaneously.

2. Evaluation of the Effects of Shampooing or Water Immersion on the Initial and Residual Efficacy of Imidacloprid for Flea Control on Dogs. Report # 74792

Purpose: To evaluate the initial and residual effectiveness of imidacloprid on dogs following shampooing or water immersion.

Investigator: Ron Everett, Ph.D.

Study Location: AgResearch Consultants, Inc. (ARC)
Greenbriar, AR

Animals: 24 dogs (13 females and 11 males), 2 to 11 years of age, 8 per group (Group 1 had 5 females and 3 males, groups 2 and 3 had 4 females and 4 males).

Dosage Groups:
Group 1: Imidacloprid 10 mg/kg: Shampooed 4 days post-treatment
Group 2: Imidacloprid 10 mg/kg: Water immersion weekly post-treatment
Group 3: Vehicle: ½ shampooed 4 days post-treatment ½ immersed in water weekly post-treatment

Route of Administration: Topical

Frequency of Treatment: Once

Duration of Study: 35 days

Study Design: Dogs in group 1 were shampooed with a non-medicated shampoo 4 days post-treatment. Group 2 dogs on day 4 post-treatment were immersed in a tank of tap water for one minute and allowed to air dry. The dog's head was thoroughly wetted three times during the immersion procedure. The water immersion was repeated at weekly intervals on Days 4, 11, 18, 25, and 32. Dogs in group 3 were divided into two groups. Half were shampooed on day 4 post-treatment and the other half were immersed in water weekly. Each dog was infested with 100 adult fleas on Days –1, 6, 13, 20, 27, and 34.

Parameters Measured: Flea comb counts were performed on Days 1, 7, 14, 21, 28, and 35. All dogs were observed 30 minutes, 1, 3, and 5 hours post-treatment and daily afterward.

Results: Effectiveness of 10 mg/kg imidacloprid against *Ctenocephalides felis* after bathing or water immersion in dogs compared to the placebo is shown in the following table. The geometric mean number of fleas is shown in parenthesis.

Day	Group 1: Shampoo		Group 2: Water Immersion		Control Shampoo	Control Water Immersion
1	100%	(0)	100%	(0)	(94.3)	(66.6)
7	98.9%	(0.9)	99.8%	(0.1)	(90.0)	(74.3)
14	97.7%	(2.2)	99.4%	(0.5)	(94.5)	(85.8)
21	94.4%	(5.4)	95.7%	(3.8)	(95.6)	(87.5)
28	96.3%	(3.7)	96.7%	(2.7)	(100.4)	(83.9)
35	71.4%	(25.5)	86.8%	(12.2)	(89.1)	(92.5)

Conclusions: Imidacloprid applied topically as a single dose of 10 mg/kg was from 94.4% to 100% effective against adult flea infestations for 28 days after shampooing 4 days post-treatment or immersion in water weekly post-treatment. This study will support the labeling statement: Shampooing or water immersion 4 days after treatment will not reduce the effectiveness of Advantage DUO against flea infestations.

Adverse Reactions: None reported.

D. EFFECTIVENESS STUDIES AGAINST HEARTWORMS:

1. Efficacy of Topically Applied Imidacloprid + Ivermectin Against 30 and 45 Day Old Heartworm Infections of Dogs. Report #75123

Purpose: The objective of this study was to establish and compare the effectiveness and safety of three topically-applied imidacloprid (10 mg/kg) + ivermectin (0, 80, and 160 mcg/kg) formulations against 30 and 45-day old heartworm (*Dirofilaria immitis*) larval infections of dogs.

Study Director: Dwight Bowman MS, Ph.D.

Study Location: Cheri-Hill Research and Development

Stanwood, MI

Animals: 48 beagles (24 males and 24 females), 20 – 22 weeks old, 8 dogs per group. Dogs were group housed by sex and treatment.

Dosage Groups:
Group 1: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin (0.1 mL/kg), 30 days post-infection
Group 2: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin (0.1 mL/kg), 45 days post-infection
Group 3: 10 mg/kg imidacloprid + 160 mcg/kg ivermectin (0.1 mL/kg), 30 days post-infection
Group 4: 10 mg/kg imidacloprid + 160 mcg/kg ivermectin (0.1 mL/kg), 45 days post-infection
Group 5: 10 mg/kg imidacloprid control, 30 days post-infection
Group 6: 10 mg/kg imidacloprid control, 45 days post-infection

Route of Administration: Topical, at one spot on the skin of the neck (dorsal midline)

Frequency of Treatment: Once

Duration of Study: 157 days

Study Design: The dogs were acclimated for 6-12 weeks prior to infection with *D. immitis* infective larvae. Each dog was administered approximately 50 infective larvae on Day 0. Dogs were treated either 30 or 45 days post-infection.

Parameters Measured: Each dog was observed at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-treatment. They were observed twice daily thereafter. Dogs were retested for heartworms on Days 120 and 150 using both the modified Knott's test and the ELISA test. The dogs were euthanized and necropsied on Day 157. Heartworms were counted and sexed.

Results: No heartworms were recovered from dogs in Groups 1, 2, 3, and 4 on Day 157. The mean number of adult heartworms in Group 5 was 27.8 worms/dog and in Group 6 was 24 worms/dog.

Mean Number of Heartworms Recovered and % Effectiveness

Treatment Group	# of Heartworms	% Effectiveness
1	0	100
2	0	100
3	0	100
4	0	100
5	27.80	N/A
6	24.02	N/A

Conclusion: The combination product, imidacloprid + ivermectin, at two different concentrations, 80 mcg/kg, and 160 mcg/kg, was 100% effective against preventing heartworm disease when administered either 30 or 45 days post-infection.

Adverse Reactions: Several dogs in all treatment groups had stiff hair and white residue at the treatment site which resolved spontaneously by 24 hours.

2. Effect of Post-Treatment Bathing/Shampooing on the Efficacy of Topically Applied Imidacloprid + Ivermectin Against 29 and 36-Day Old Heartworm Infections of Dogs. Report #75124:

Purpose: To determine the effect of post-treatment water immersion or shampooing, on the prophylactic effectiveness of topically applied imidacloprid + ivermectin against 29 and 36-day old heartworm (*Dirofilaria immitis*) infections of dogs.

Study Director: Robyn L. Slone

Study Location: Professional Laboratory and Research
Corapeake, NC

Animals: 40 beagles (17 males and 23 females), 11 – 26 months old. 4 dogs per group. Dogs were individually housed during treatment and 7 days post-treatment. Dogs were housed in groups of 3-5.

Dosage Groups:

Group	Treatment	Treatment Day	Water Immersion (WI)/ Shampoo Time/Day
1	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	0	WI 4 Hrs. Post-treatment
2	10 mg/kg imidacloprid + 80mcg/kg ivermectin	7	WI 4 Hrs. Post-treatment
3	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	0	WI 24 hrs, 7, 14, 21, & 28 Days Post-treatment
4	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	7	WI 24 hrs, 7, 14, 21, & 28 Days Post-treatment
5	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	0	Shampoo 4 Days Post-treatment
6	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	7	Shampoo 4 Days Post-treatment
7	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	0	Shampoo 7 Days Post-treatment
8	10 mg/kg imidacloprid + 80 mcg/kg ivermectin	7	Shampoo 7 Days Post-treatment
9	Vehicle	0	WI 24 hrs, 7, 14, 21, & 28 Days Post-treatment
10	Vehicle	7	WI 24 hrs, 7, 14, 21, & 28 Days Post-treatment

Route of Administration: Topical, at one spot on the skin of the neck (dorsal midline)

Frequency of Treatment: Once

Duration of Study: 154 days

Study Design: The dogs were acclimated for 55-57 days prior to infection with *D. immitis* infective larvae. Dogs were tested on Day –32 for heartworms using both the modified Knott's test and the ELISA test. Each dog was administered approximately 50 infective larvae on Day –30. Dogs were treated either 29 or 36 days post-infection. For bathing/shampooing, the dog's coat was wetted, shampoo was applied, and lathered freely. The shampoo was allowed to remain in contact with skin and hair coat for 2-3 minutes. The dog was rinsed well and the procedure was repeated. For water immersion, the dog's entire body (up to but not including the face), was immersed in a deep tank of clean, tepid water for approximately 2 minutes.

Parameters Measured: Each dog was observed at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-treatment. They were observed twice daily thereafter. Dogs were retested for heartworms on Day 120 using both the modified Knott's test and the ELISA test. The dogs were euthanized and necropsied on Day 154. Heartworms were counted and sexed.

Results: No heartworms were recovered from dogs in Groups 1, 2, 3, and 4 on Day 157. The mean number of adult heartworms in Group 9 and 10 combined was 22.7 worms/dog.

Mean Number of Heartworms Recovered and % Effectiveness

Treatment Group	# of Heartworms	% Effectiveness
1	0	100
2	0	100
3	0	100
4	0	100
5	0	100
6	0	100
7	0	100
8	0	100
9	25.5	N/A
10	27.25	N/A

Conclusion: The effectiveness of 10 mg/kg imidacloprid + 80 mcg/kg ivermectin was 100% in preventing heartworm disease after either shampooing 4 days post-treatment or water immersion 4 hours post-treatment. This study will support the labeling statement: Shampooing 4 days after treatment or water immersion 4 hours after treatment will not reduce the effectiveness of Advantage DUO in prevention of heartworm disease.

Adverse Reactions: One dog in treatment group 8 vomited 3 hours post-treatment and one dog in treatment group 10 vomited 6 hours post treatment. Several dogs in various treatment groups had greasy, stiff hair and/or white residue at the treatment site which resolved spontaneously by 24 hours.

III. TARGET ANIMAL SAFETY STUDIES

A. Evaluation of the Safety of Imidacloprid/Ivermectin in Young Dogs. Report #75084

Purpose: To provide information regarding the safety of an investigational new animal drug (imidacloprid/ivermectin) when administered dermally to young dogs.

Investigator: Robyn Slone

Study Location: Professional Laboratory and Research Services, Inc.
Corapeake, NC

Animals: 32 beagle puppies (16 males and 16 females), 53 – 59 days old, 2.8 to 5.2 lbs. 8 dogs per group.

Dosage Groups: Dosed based on weight ranges.

Group 1: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 1X
Group 2: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 3X
Group 3: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 5X
Group 4: control (baby oil), 5X volume

Route of Administration: Topical

Frequency of Treatment: Once weekly x 8 times

Duration of Study: 65 days

Study Design: Dogs were acclimated for 6 to 14 days prior to the start of the study. Each dog had a physical exam, was weighed and had blood drawn for hematology and clinical chemistry during this time. All dogs were tested for the presence of heartworms by the antigen and modified Knott's test. Dogs were treated on Days 0, 7, 14, 21, 28, 35, 42, and 49.

Parameters Measured: Clinical observations were conducted at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-treatment on Days 0, 28, and 56. Beginning on Day 1 clinical observations were performed twice daily. The application site was observed once daily for signs of irritation. The dogs were weighed again on Days 0, 7, 14, 28, 35, 42, 49, 56, and 63. Food consumption was recorded daily for each puppy beginning on study day –9 through day 64. Blood was drawn from each dog on study days -1, 1, 7, 14, 22, and 63 for hematology and clinical chemistry profiles. Each dog received a physical exam on Days 1 and 7. Necropsies were conducted on Days 63 - 65 and gross pathologic examination performed. Bone marrow smears were made and tissues from the 5X and control group animals were processed for histopathology.

Results: *Application site:* Greasy hair and colored deposits were noted in every animal treated with the test article at one time during the study. The control group had greasy hair only. Two out of eight animals in the 3X treated group had hair loss and reddening/irritation at the application site on study days 22-49. Two dogs had reddening/irritation and/or scabs at the application site. 3/8 dogs in the control group had hair loss at the application site also for a shorter period of time.
Gastrointestinal: Two dogs treated with the 3X dose and one dog treated with the 5X dose vomited within hours of receiving the test article.
Several dogs treated with 1X, 3X, and 5X had bouts of diarrhea closely associated to treatment. One control dog had diarrhea 24 hours after treatment.
Hematology and Chemistry: One dog in the 1X group, 3/8 dogs in the 3X group, and one dog in the 5X group had a leukocytosis with a concomitant neutrophilia. No animals in the control group developed increases in WBC.

Body Weights: No differences were noted between groups.

Food Consumption: No differences were noted between groups.

Conclusions: Transient vomiting, diarrhea, and leukocytosis were associated with administration of imidacloprid + ivermectin at one, three and five times the recommended dosage. Greasy hair occurred at the application site at all dosage levels including the control group. Alopecia and erythema occurred at the application site at 3 times the recommended dosage. Alopecia also occurred in the control group.

B. Dermal Safety Study with Imidacloprid/Ivermectin in the Ivermectin-Sensitive Collie. Report #75087

Purpose: This nonclinical laboratory investigation was designed to provide information regarding the safety of an investigational new animal drug, imidacloprid/ivermectin, when used in the ivermectin-sensitive collie.

Investigator: Douglas E. Hutchens, D.V.M., M.S.

Study Location: University of Illinois
Urbana, IL

Animals: 15 ivermectin-sensitive collies (5 males and 10 females) approximately 8 months to 7 years old, 3 dogs in Group 1, 6 dogs in Groups 2 and 3.

Dosage Groups:

Group 1:	10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 3X (3 dogs)
Group 2:	10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 5X (6 dogs)
Group 3:	baby oil, 5X control (6 dogs)

All dogs received 3X or 5X the maximum dosage within the recommended dermal dose range for the animal's body weight. An oral safety study in ivermectin-sensitive collies was not conducted because of the known oral toxicity of ivermectin at the 1x dose of Advantage DUO.

Route of Administration: Topical

Frequency of Treatment: Group 1 (3X) was treated on day 0 with the test article, while groups 2 and 3 were treated with baby oil at 3X. After observations with no adverse effects, group 1 (3X) was treated again on days 28 and 56. Groups 2 (5X) and 3 (control, 5X) were treated as outlined above in the dosage groups on days 28, 56 and 84. Therefore dogs were treated once a month for 3 months.

Duration of Study: 98 days

Study Design: Collies were screened for ivermectin sensitivity prior to arrival at the University of Illinois. Dogs were acclimated for a minimum of 14 days prior to the start of the study. Each dog had a physical exam, was weighed and had blood drawn for hematology and clinical chemistry during this time. All dogs were tested for the presence of heartworms by the antigen and modified Knott's test.

Parameters Measured: Clinical observations were conducted at 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-treatment. Dogs were observed twice daily starting on day –7 and were observed twice daily on non-treatment days. The application site was examined twice a day for the first three days then once a day thereafter. The dogs were weighed on Days 0, 28, 56, and 84.

Results: One dog treated with 5X imidacloprid/ivermectin developed a hot spot along the back five days after treatment. It can not be determined if this was related to treatment. Two dogs in the control group developed hot spots 4 days and 8 days post treatment at the base of the tail and on the right hip respectively. These were not related to treatment.

Conclusions: Dermal application of imidacloprid/ivermectin at 3X and 5X the maximum recommended dosage did not produce clinical signs of ivermectin toxicosis in ivermectin-sensitive collies. One dog developed a hot spot possibly related to treatment.

C. Dermal Dose Tolerance Study with Imidacloprid/Ivermectin in the Beagle Dog Report #75086-1

Purpose: To demonstrate the safety of imidacloprid/ivermectin when administered dermally in the canine at ten times (10X) the recommended dermal unit dosage of 10 mg/kg imidacloprid and 80 mcg/kg ivermectin.

Investigator: Elizabeth I. Evans, DVM

Study Locations: Midwest Research Institute
Kansas City, MO

Animals: 16 beagles (8 males and 8 females), approximately 8 to 11 months old, 8 dogs per group.

Dosage Groups:

Group 1: 10 mg/kg imidacloprid + 80mcg/kg ivermectin (10X)
Group 2: baby oil (control)

Route of Administration: Topical

Frequency of Treatment: Once daily for three days

Duration of Study: 14 days

Study Design: Dogs were acclimated for a minimum of 14 days prior to the start of the study. Each dog had a physical exam, was weighed and had blood drawn for hematology and clinical chemistry during this time. All dogs were tested for the presence of heartworms by the antigen and modified Knott's test.

Parameters Measured: Clinical observations were conducted at 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-treatment. Beginning on Day 3 clinical observations were performed twice daily afterward. The application site was examined twice a day for the first three days then once a day thereafter. The dogs were weighed again on Day 14. Blood was drawn from each dog on study days 4 and 14 (after dosing was completed) for hematology and clinical chemistry profiles.

Results: *Application site*: Erythema at the application site was observed in two dogs treated with the test material which resolved after twenty-four hours. Two dogs treated with the test article had pinna erythema which resolved after several days. Three dogs treated with baby oil had pinna erythema which lasted most of the study. All dogs including the treated and control dogs had white material present on the hair at least once during the three days of dosing for approximately 24 hours after the dose was administered. Three dogs (two in the treated group, and one in control group) were observed scratching at the application site within 24 hours post-dosing.

Vomiting: Two dogs treated with the test article vomited within 24 hours after the test article. No control dogs vomited during this time frame.

Clinical Pathology: One male dog in the treated group had an elevated serum amylase on Day 4. One dog treated with the test material on day 4, had an elevated WBC count characterized by increased neutrophils and decreased lymphocytes.

Conclusions: Administration of ten times the recommended topical dosage for three consecutive days produced erythema of the application site and of the pinna, white residue and pruritus at the application site, vomiting, and a transient elevation of amylase and leukocytosis with neutrophilia and lymphopenia in beagle dogs.

D. Evaluation of the Safety of Advantage®/KB100 in Spot-on in Dogs Naturally Infected with Heartworms (*Dirofilaria immitis*). Report #75083

Purpose: To provide information regarding the safety of an investigational new animal drug when administered dermally to dogs with naturally-acquired heartworm (*Dirofilaria immitis*) infection at one (1X) or five (5X) times the recommended unit dosage.

Investigator: Robyn Slone

Study Locations: Professional Laboratory and Research Services, Inc.
Corapeake, NC

Animals: 28 mixed breed dogs (14 males and 14 females), > 6 months old, and 8.8 to 28.5 kg. 10 dogs in Group 1 (5 males and 5 females), 9 dogs in Group 2 (5 males and 4 females), 9 dogs in Group 3 (4 males and 5 females). Dogs were individually housed.

Dosage Groups: Dosed based on weight ranges.

Group 1: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 1X
Group 2: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin, 5X
Group 3: control (baby oil)

Route of Administration: Topical

Frequency of Treatment: Once monthly x 3

Duration of Study: 61 days

Study Design: Dogs were acclimated for 6 to 14 days prior to the start of the study. Each dog had a physical exam, was weighed and had blood drawn for hematology and clinical chemistry during this time. All dogs were tested for the presence of heartworms by the antigen and modified Knott's test.

Parameters Measured: Clinical observations were conducted at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-treatment on Days 0, 28, and 56. Beginning on Day 1 clinical observations were performed twice daily. The application site was observed once daily. The dogs were weighed on Days 28 and 56. Blood was drawn from each dog on study days 1, 27, 55, and 57 for modified Knott's test for microfilariae and canine heartworm antigen test. Each dog received a physical exam on Day 57. Necropsies were conducted on Day 61 and adult heartworms were counted that were found in the pleural cavity, pre-cava, right atrium, right ventricle, and pulmonary arteries and branches.

Results: One dog in Group 1 vomited one time 8 hours post-treatment which may be related to treatment. No other adverse reactions were recorded that could be due to the treatment in heartworm positive dogs up to 5X the recommended dosage.
Mean changes from baseline in Group 1(1X) and Group 2 (5X) animals compared to mean changes from baseline for concurrent control animals were observed in amylase, creatinine and alkaline phosphatase values. One dog in Group 2 (5X) did not have any adult heartworms at the time of necropsy, despite being positive for microfilariae during the study. It was not included in the safety evaluation. Colored deposits on the tips of hair were seen at the application site.

Conclusions: Administration of one or five times the recommended topical dosage in heartworm positive dogs did not produce any signs of an anaphylactic reaction; however, one dog vomited 8 hours post-treatment in the 1X group. An increase in amylase, creatinine, and alkaline phosphatase was noted in the 1X and 5X groups. A colored residue at the application site was also observed.

E. Single-Dose Oral Safety Study with Imidacloprid/Ivermectin in the Beagle Dog Report #75085-1

Purpose: To demonstrate the safety of 10% Imidacloprid/0.08% Ivermectin when administered orally in the canine at the recommended dermal dose (1X).

Investigator: Elizabeth I. Evans, DVM

Study Location: Midwest Research Institute
Kansas City, MO

Animals: 16 beagles (8 males and 8 females), approximately 4 to 7 months old, 8 dogs per group.

Dosage Groups:

Group 1: 10 mg/kg imidacloprid + 80 mcg/kg ivermectin
Group 2: saline

Route of Administration: Oral by gavage

Frequency of Treatment: Single treatment

Duration of Study: 14 days

Study Design: Dogs were acclimated for a minimum of 14 days prior to the start of the study. Each dog had a physical exam, was weighed and had blood drawn for hematology and clinical chemistry during this time. All dogs were tested for the presence of heartworms by the antigen and modified Knott's test.

Parameters measured: Clinical observations were conducted at 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-treatment, and then twice daily afterward. The oral cavity was examined approximately 6 and 24 hours post-dosing.

Results: Six out of eight dogs receiving the test article vomited within the first hour post-dosing with one dog vomiting up to 3 hours post-dosing (this dog was redosed after the first dose was administered due to vomiting). Vomiting was directly related to the test article. Several dogs in the treated and control group had soft stools at various times of the study.

Conclusions: A single oral dose of 10 mg/kg imidacloprid + 80 mcg/kg ivermectin administered at the recommended dermal dose causes immediate transient vomiting (within 3 hours).

F. Clinical Safety Evaluation of Imidacloprid + KB 100 (Ivermectin) Applied Dermally to Dogs. Report #75193

Purpose: To assess the safety of dermally-applied Imidacloprid + KB100 (ivermectin) in dogs when administered by clients/owners under the conditions of actual field-use.

Investigators and Locations:

Lisa Arthur, DVM
Sunshine Animal Hospital
8008 W. Waters Ave.
Tampa, FL 33615

Roger Becker, DVM
Independence Animal Hospital
300 S Noland
Independence, MO 64050

Richard Mauldin, DVM
Hillcrest Animal Hospital
5720 S. Penn
Oklahoma City, OK 73119

Craig Staehle, DVM
Cave Springs Animal Hospital
251 Jungermann Rd.
St. Peters, MO 63376

Animals and Household Distributions: A total of 243 dogs from 120 different households were enrolled in the study. Of these, 242 client-owned animals (146 males and 96 females) completed the study. 169 dogs were treated with the test article and 73 were treated with the control. One dog (a collie) was withdrawn due to owner concern about the potential safety of the product. Fifty-seven breeds were represented with the predominant breeds being mixed (81 dogs), Shetland Sheepdog (17 dogs), English Bulldog (10 dogs), Yorkshire Terrier (9 dogs), Labrador Retriever (8 dogs), Dachshund (7 dogs), Australian Shepherd (6 dogs), and Jack Russell Terrier (6 dogs). Also included were Collie crosses (7 dogs), Shetland sheepdog crosses (3 dogs), Australian Shepherd crosses (1 dog), and Border Collie crosses (1 dog).

The age range was from 3 months old to 15 years old for dogs treated with the test article. The weights ranged from 4.6 to 129 lbs.

Dosage Groups:

Group 1: imidacloprid 10 mg/kg + ivermectin 80 mcg/kg (Test Group)
Group 2: Advantage® (imidacloprid) 10 mg/kg + Heartgard ® (ivermectin) 6 mcg/kg (Control Group)

Route of Administration: Topical for Group 1, topical and oral for Group 2

Frequency of Treatment: Once monthly x 3

Duration of Study: 90 days

Inclusion Criteria: Heartworm and microfilariae negative, 7 weeks of age or older, single or multi-dog households, breeds genetically predisposed to idiosyncratic ivermectin sensitivity (Collies, border collies, Shetland sheepdogs, Australian shepherds, and their crosses) encouraged.

Exclusion Criteria: Dogs with patent heartworm infections, enrollment of severely compromised and/or terminal patients was discouraged.

Randomization: Unique randomization schedules were generated for each clinical site. Randomization schedules were designed to ensure that all entrants from each of the four distinct household/breed combinations (single-dog household/non-collie, single-dog household/collie-lineage, multiple-dog household/non-collie, and multiple-dog household with one or more dogs of collies-lineage) were assigned to treatments according to a 2:1 ratio (test drug:control). Qualified households (not individual dogs) were assigned to treatment groups.

Study Design: Attending veterinarians performed baseline physical examinations on all dogs. Treatments were administered by the pet owners according to written and oral instructions provided by the veterinarian. Following treatment, owners observed their pets for untoward reactions at 3 specified intervals, 30 – 60 minutes, 4 - 6 hours, and 22 – 26 hours post-treatment. Within 7 days of the final treatment, dogs were returned to the clinic for a post-study physical examination and assessment.

Results: The following tables show the adverse reactions observed for the treatment and control groups.

Observed Adverse Reactions

Observation	Imidacloprid/Ivermectin (169 dogs) # dogs (% of dogs in treatment group)	Control Group (73 dogs) # dogs (% of dogs in control group)
Pruritus	10 (5.9%)	2 (2.7%)
Diarrhea/Inappropriate Elimination	10 (5.9%)	0
White/Oily Residue	6 (3.6%)	2 (2.7%)
Vomiting	5 (2.0%)	0
Hyperactivity	3 (1.8%)	0
Anorexia	2 (1.2%)	0
Lethargy	2 (1.2%)	0
Skin Irritation/Erythema	2 (1.2%)	0
Alopecia at Application Site	1 (0.6%)	0

One dog died from congestive heart failure. It cannot be determined if treatment with imidacloprid + ivermectin contributed to her demise.

Conclusions: Adverse reactions observed related to the combination product imidacloprid + ivermectin applied once a month for three months include: pruritus, white/oily residue, alopecia, skin irritation/erythema at the application site, diarrhea, vomiting, anorexia, and hyperactivity.

IV. HUMAN 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.

Human Warnings are provided on the product label as follows: "Warnings:
For use on animals only. Keep out of the reach of children. Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Wash hands thoroughly with soap and warm water after handling. If contact with eyes occurs 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 the eye. If eye irritation persists, contact a physician. If swallowed, call 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 contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of water for 15-20 minutes. Call a poison control center or physician for treatment advice. The material safety data sheet (MSDS) provides additional occupational safety information. For a copy of the MSDS, call 1-877-258-2280.
Note to physician: Treat patient symptomatically"

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Part 514 of the implementing regulations. The data demonstrate that Advantage DUO (imidacloprid/ivermectin) Topical Solution is safe and effective in dogs for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment of flea infestations *(Ctenocephalides felis)*.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine the existence of heartworm infections and to monitor the safe use of the product.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

U.S. patent pending.

VI. LABELING

A. Package Insert
B. Calendar Reminder Stickers
C. Tube Label
D. Foil Backing for Blister Pack
E. Multi Carton
F. Shipper Label