Date of Approval: October 24, 2013

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-251

ADVANTAGE MULTI for Dogs

Imidacloprid + Moxidectin

Solution

Dogs

This supplement provides for the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs and the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis.*

Sponsored by:

Bayer HealthCare LLC
Animal Health Division

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I. GENERAL INFORMATION

A. File Number

NADA 141-251

B. Sponsor

Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

Drug Labeler Code: 000859

C. Proprietary Name

ADVANTAGE MULTI for Dogs

D. Established Name

Imidacloprid + Moxidectin

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Solution

G. Amount of Active Ingredient

10% imidacloprid + 2.5% moxidectin

H. How Supplied

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
6 x 5.0 mL tubes

I. Dispensing Status

Rx

J. Dosage Regimen

The recommended minimum dose is 4.5 mg/lb (10 mg/kg) imidacloprid and 1.1 mg/lb (2.5 mg/kg) moxidectin, once a month, by topical administration.

Dog Weight (lb)	ADVANTAGE MULTI for Dogs	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
3 – 9	ADVANTAGE MULTI 9	0.4	40	10
9.1 - 20	ADVANTAGE MULTI 20	1.0	100	25
20.1 - 55	ADVANTAGE MULTI 55	2.5	250	62.5
55.1 – 88	ADVANTAGE MULTI 88	4.0	400	100
88.1 – 110*	ADVANTAGE MULTI 110	5.0	500	125

*Dogs over 110 lbs should be treated with the appropriate combination of ADVANTAGE MULTI for Dogs tubes.

K. Route of Administration

Topical

L. Species/Class

Dog

M. Indication

ADVANTAGE MULTI for Dogs is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs. ADVANTAGE MULTI for Dogs kills adult fleas and is indicated for the treatment of flea infestations *(Ctenocephalides felis)*. ADVANTAGE MULTI for Dogs is indicated for the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*. ADVANTAGE MULTI for Dogs is also indicated for the treatment and control of the following intestinal parasites:

Intestinal Parasite	Intestinal Stage Adult	Intestinal Stage Immature Adult	Intestinal Stage Fourth Stage Larvae
Hookworm Species *Ancylostoma caninum*	X	X	X
Hookworm Species *Uncinaria stenocephala*	X	X	X
Roundworm Species *Toxocara canis*	X		X
Roundworm Species *Toxascaris leonina*	X		
Whipworm *Trichuris vulpis*	X		

N. Effect of Supplement

This supplement provides for the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs and the treatment and control of sarcoptic mange cause by *Sarcoptes scabiei* var. *canis*.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-251, dated December 20, 2006, contains dosage characterization information for dogs.

B. Substantial Evidence

1. For the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs (induced infection):

   a. Title:

   "Laboratory Evaluation of the Efficacy of 10% Imidacloprid + 2.5% Moxidectin Topical Solution for the Treatment of *Dirofilaria immitis* Circulating Microfilariae in Dogs" (Study Number: 152.222)

b. Investigator:

John W. McCall, PhD
Athens, GA

c. Study Design:

(1) Objective:

To evaluate the effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution administered at the minimum labeled dose of 0.1 mL/kg, for the treatment of circulating *D. immitis* microfilariae in dogs.

(2) Study Animals:

Twenty Beagle dogs (10 male and 10 female), approximately 1.2 years of age, weighing 9.3 to 12.6 kg; 10 dogs per treatment group. Each dog was implanted with 10 pairs of adult heartworms (*D. immitis*) on Study Day -82. The dogs enrolled in the study had Heartworm Disease Classifications of 1 and 2. Prior to enrollment, dogs were evaluated with regard to status of heartworm disease and placed into four distinct Heartworm Disease Classifications, 1 – 4, based on the American Heartworm Society publication, "2005 Guidelines for the Diagnosis, Prevention, and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs" (www.heartwormsociety.org).

(3) Treatment Groups:

Group 1: 10% imidacloprid + 2.5% moxidectin topical solution
Group 2: Placebo control (mineral oil)

(4) Dose and Route of Administration:

0.1 mL/kg bodyweight applied topically on the skin between the shoulder blades on Study Days 0 and 28.

(5) Measurements and Observations:

A modified Knott's test was conducted on Study Days -7, -6, and -5 to establish pre-treatment microfilariae counts. Complete blood counts, serum chemistries, urine analyses, and chest radiographs were conducted pre-treatment. Dogs were observed for adverse reactions at 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-treatment on Study Days 0 and 28. Dogs were observed once daily on all other post-treatment study days. Microfilariae counts were conducted on Study Days 1, 2, 3, 7, 14, 21, 28, 35, and 42. Study Day 42 was the primary end point and Study Day 28 was a secondary end point.

(6) Statistical Methods:

The microfilariae counts were transformed, log(data+1), and analyzed using an analysis of covariance as a randomized complete block design with a one-way treatment structure with two levels. The statistical model included treatment as a fixed effect, block as a random effect, and the mean pre-treatment microfilariae counts as the covariate. If the treatment main effect was not statistically significant (p-value > 0.05) no additional analyses were conducted. If the treatment main effect was statistically significant (p-value ≤ 0.05) a pair-wise comparison was conducted using the least squares means and a two-sided test at alpha = 0.05.

Decision Rule: The decision rule was structured to be evaluated first on Day 42 and if the following three criteria were met, evaluated on Day 28.

The 10% imidacloprid + 2.5% moxidectin topical solution was judged effective if the following three criteria were met.

(a) The control group demonstrated an adequate infection of ≥ 300 mf/mL in at least 6 animals.[1]

(b) A ≥ 90% reduction in the treated animal microfilariae (mf) counts compared to the control group. Percent reduction is defined as:

mf% reduction = [(GM (Control)- GM(Treated)) ÷GM (Control)] X 100

where GM is the geometric mean. In the case of zero counts the GM was calculated on transformed data, log(data+1), and GM = exp(mean(log(data+1)))−1.

(c) A statistically significant least squares mean comparison (p-value < 0.05) using a two-sided test on the log microfilariae counts.

[1] In a study conducted for the original approval of ADVANTAGE MULTI for Dogs (NADA 141-251, Study 150.875) to investigate the safety of ADVANTAGE MULTI for Dogs (10% imidacloprid + 2.5% moxidectin topical solution) in heartworm positive dogs, 8 pairs (8 male and 8 female) adult heartworms were transplanted into 24 Beagle dogs. The mean microfilariae (mf) count was 299 mf/mL 60 days post-implantation. At necropsy 98 days post-implantation, 105 adult worms were recovered from untreated dogs, for an average heartworm infection of 13 adult worms per dog. This study demonstrated that approximately 300 mf/mL corresponds to a known level of adult heartworm infection in dogs. Therefore, 300 mf/mL was selected to define the adequacy of infection for studies 150.222 and 150.224.

d. Results:

Effectiveness against circulating microfilariae infections was determined by comparing the geometric mean number of microfilariae in the control group with that of the treated group. Microfilariae reduction on Study Day 28 and on Study Day 42 was 99.9%. Log microfilariae counts were significantly lower in treated versus control dogs on Study Days 28 and 42 (p-value < 0.05) using a separate analysis of covariance for each study day. The results are summarized in Table 1 below.

Table 1: Summary of Results for Study Days 28 and 42

Study Day	Percent Reduction	No. Control Dogs **≥ 300** mf*/mL	Geometric Mean (mf* count) Control / Treated	Control Dog mf Count Range	p-Value
28	99.9	10/10	12854.6 / 11.1	2,750 – 31,500	< 0.05
42	99.9	9/10	6636.4 / 7.1	0 – 27,500	< 0.05

*mf=microfilariae

e. Adverse Reactions:

No adverse reactions were reported in this study.

f. Conclusion:

Treatment of adult dogs with induced infections of *D. immitis* with 10% imidacloprid + 2.5% moxidectin topical solution at 0.1 mL/kg body weight was >99% effective in reducing microfilariae counts by Study Day 42.

2. For the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs (natural infection):

a. Title:

"Laboratory Evaluation of the Efficacy of 10% Imidacloprid + 2.5% Moxidectin Topical Solution for the Treatment of *Dirofilaria immitis* Circulating Microfilariae in Dogs" (Study Number: 152.224)

b. Investigator:

Dwight Bowman, PhD
Stanwood, MI

c. Study Design:

(1) Objective:

To evaluate the effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution given at the minimum labeled dose of 0.1 mL/kg, for the treatment of circulating *D. immitis* microfilariae in dogs.

(2) Study Animals:

Twenty-two adult, random sourced, mixed breed dogs > 6 months of age (10 males and 12 females), weighing between 12 and 45 kg; 11 dogs per treatment group. Each dog was naturally infected with adult heartworms. The dogs enrolled in the study had Heartworm Disease Classifications of 1 and 2.

(3) Treatment Groups:

Group 1: 10% imidacloprid + 2.5% moxidectin topical solution
Group 2: Placebo control (mineral oil)

(4) Dose and Route Administration:

0.1 mL/kg bodyweight applied topically on the skin between the shoulder blades on Study Days 0 and 28.

(5) Measurements and Observations:

A modified Knott's test was conducted on Study Days -8, -7, -6, and -5 to establish pretreatment microfilariae counts. Complete blood counts, serum chemistries, urine analyses, and chest radiographs were conducted pre-treatment. Dogs were observed for adverse reactions at 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-treatment on Study Days 0 and 28. The dogs were observed once daily on all other post-treatment study days. Microfilariae counts were conducted on Study Days 1, 2, 3, 7, 14, 21, 28, 35, and 42. Study Day 42 was the primary end point and Study Day 28 was a secondary end point.

(6) Statistical Methods:

The microfilariae counts were transformed, log(data+1), and analyzed using an analysis of covariance as a randomized complete block design with a one-way treatment structure with two levels. The statistical model included treatment as a fixed effect, block as a random effect, and the mean pre-treatment microfilariae counts as the covariate. If the treatment main effect was not statistically significant (p-value > 0.05) no additional analyses were conducted. If the treatment main effect was statistically significant (p-value ≤ 0.05) a pair-wise comparison was conducted using the least squares means and a two-sided test at alpha = 0.05.

Decision Rule: The decision rule was structured to be evaluated first on Study Day 42 and if the following three criteria were met, evaluated on Study Day 28.

The 10% imidacloprid + 2.5% moxidectin topical solution was judged effective if the following three criteria were met.

(a) The control group demonstrated an adequate infection of ≥ 300 mf/mL in at least 6 animals.

(b) A ≥ 90% reduction in the treated animal microfilariae (mf) counts compared to the control group. Percent reduction is defined as:

mf% reduction = [(GM (Control)- GM(Treated)) ÷GM (Control)] X 100

where GM is the geometric mean. In the case of zero counts the GM was calculated on transformed data, log(data+1), and

GM = exp(mean(log(data+1)))−1.

(c) A statistically significant least squares mean comparison (p-value < 0.05) using a two-sided test on the log microfilariae counts.

d. Results:

Effectiveness against circulating microfilariae infections was calculated by comparing the geometric mean number of microfilariae in the control group with that of the treated group. Microfilariae reduction was 100% on Study Day 28 and ≥ 99% on Study Day 42. Log microfilariae counts were significantly lower in treated versus control dogs on Study Days 28 and 42 (p-value < 0.05) using a separate analysis of covariance for each study day. The results are summarized in Table 2 below.

Table 2: Summary of Results for Study Days 28 and 42

Study Day	Percent Reduction	No. Control Dogs ≥ 300 mf*/mL	Geometric Mean (mf* Count) Control / Treated	Control Dog mf Ranges	p-Value
28	100.0	10/11	4127.4 / 2.7	200 – 27,450	< 0.05
42	99.9	10/11	3906.4 / 0.3	250 – 27,450	< 0.05

*mf=microfilariae

e. Adverse Reactions:

No adverse reactions were reported in this study.

f. Conclusion:

Treatment of dogs naturally infected with *D. immitis* with 10% imidacloprid + 2.5% moxidectin topical solution was >99% effective in reducing microfilariae counts by Study Day 42.

3. For the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*.

a. Title:

"Laboratory Evaluation of the Efficacy of 10% Imidacloprid + 2.5% Moxidectin Topical Solution Against *Sarcoptes scabiei* var. *canis* in Dogs" (Study Number 152.179)

b. Investigator:

Jennifer Ketzis, PhD
Carrentrila, Ireland

c. Study Design:

(1) Objective:

To evaluate the effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution at the minimum label dose of 0.1 mL/kg for the treatment and control of *Sarcoptes scabiei* var. *canis* in adult dogs.

(2) Study Animals:

Thirty-two purebred or mongrel adult dogs (13 females, 19 males) with naturally acquired *Sarcoptes scabiei* var. *canis* infestations, weighing 8.1 to 32.9 kg; 8 dogs per treatment group.

(3) Treatment Groups:

Group 1: Placebo control (mineral oil) on Study Day 0
Group 2: 10% imidacloprid + 2.5% moxidectin topical solution on Study Day 0
Group 3: Placebo control (mineral oil) on Study Days 0 and 28
Group 4: 10% imidacloprid + 2.5% moxidectin topical solution on Study Days 0 and 28

(4) Dose and Route of Administration:

0.1 mL/kg bodyweight applied topically on the skin between the shoulder blades on Study Days 0 (all groups) and 28 (Groups 3 and 4).

(5) Measurements and Observations:

The presence of live mites (larvae, nymphs, adults) was confirmed by skin scraping for each dog prior to study inclusion. The dogs were randomized and allocated to four treatment groups by Study Day -1 or 0 pre-treatment geometric mean mite counts. Post-treatment skin scrapings for evaluation of live mites were performed on Study Days 14, 28, 42, and 56. Clinical skin lesion scores (alopecia, pruritus, erythema, pyoderma, papules, scaling/crusting) were recorded on the same day as the mite counts as a secondary variable.

(6) Statistical Methods:

Primary effectiveness determination following a single treatment of 10% imidacloprid + 2.5% moxidectin topical solution was based on the percent reduction of geometric mean mite counts for Group 2 dogs compared to the geometric mean mite counts for Group 1 dogs on Study Day 28. Primary effectiveness determination following treatments with 10% imidacloprid + 2.5% moxidectin topical solution

was based on the percent reduction of geometric mean mite counts for Group 4 dogs compared to the geometric mean mite counts for Group 3 dogs on Study Day 56. Clinical skin lesion scores were recorded on Study Days 14, 28, 42 and 56.

d. Results:

A single treatment on Study Day 0 with 10% imidacloprid + 2.5% moxidectin topical solution provided 93.4% reduction in live mites on Study Day 28. Treatment on Study Day 0 and 28 with 10% imidacloprid + 2.5% moxidectin topical solution provided 100% reduction in live mite counts on Study Day 56. The groups treated with 10% imidacloprid + 2.5% moxidectin topical solution had a greater improvement in clinical skin lesion scores compared to the placebo groups.

e. Adverse Reactions:

No adverse reactions were reported in this study.

f. Conclusions:

Treatment with 10% imidacloprid + 2.5% moxidectin topical solution was effective against naturally acquired *Sarcoptes scabiei* var. *canis* infestations in adult dogs. A single treatment of 10% imidacloprid + 2.5% moxidectin topical solution provided 93.4% reduction in live mites at Study Day 28 and two treatments of 10% imidacloprid + 2.5% moxidectin topical solution administered 28 days apart provided 100% reduction in live mites at Study Day 56.

4. For the treatment and control of *Sarcoptes scabiei* var. *canis* infestations in dogs:

a. Title:

"Clinical Evaluation of the Safety and Efficacy of 10% Imidacloprid + 2.5% Moxidectin Topical Solution Against *Sarcoptes scabiei* var. *canis* in Dogs" (Study Number 152.180)

b. Investigators:

Lynn Buzhardt, DVM
Zachary, LA

Bill Campaigne, DVM
Seguin, TX

Laird Laurence, DVM
Fredericksburg, TX

Richard Mauldin, DVM
Oklahoma City, OK

Roger Sifferman, DVM
Springfield, MO

c. Study Design:

(1) Objective:

To evaluate the safety and effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution at the minimum label dose of 0.1 mL/kg for the treatment and control of *Sarcoptes scabiei* var. *canis* in dogs.

(2) Study Animals:

A total of 137 dogs (73 male, 62 female, and 2 unknown, 2 months to 12.5 years of age, weighing 3.0 to 231.5 pounds) from 63 households were enrolled in the study. Of the 137 dogs enrolled, 62 dogs were included in the effectiveness evaluation (39 were treated with the investigational product, 10% imidacloprid + 2.5% moxidectin topical solution, and 23 were treated with an active control, selamectin 6% or 12%). The safety evaluation included 135 out of 137 dogs (2 dogs did not complete the study for reasons not related to treatment).

(3) Enrollment Criteria:

Dogs with at least five live sarcoptic mites (adult, nymph, or larvae) obtained from up to 10 skin scraping sites and skin lesions typical of sarcoptic mange infestation were eligible for the study. Only one dog per household could qualify for the effectiveness evaluation; however, multiple dogs from one household were required to be enrolled in the safety evaluation and were treated with the same product.

(4) Treatment Groups:

Dogs were randomly assigned to the treatment group, 10% imidacloprid + 2.5% moxidectin topical solution, or the control group, selamectin. The ratio of households in the treatment group to households in the control group was 1.7:1.0.

(5) Dose and Route of Administration:

Both the investigational and control products were commercially packaged and dispensed in pre-filled applicator tubes. The products were administered topically according to package instructions. Dogs were treated twice, approximately 28 days apart. Both treatments were administered by the owner in the presence of clinic personnel.

(6) Measurements and Observations:

Physical examinations: Investigators conducted physical examinations at study enrollment (Study Day 0) and study end (Study Day 56).

Owner observations: Owners observed their dog(s) in the 24 hours following treatment, and findings were recorded.

Deep skin scraping: Post-treatment skin scrapings for mites during the follow up visits on Study Days 28 and 56 were obtained from the same skin sites evaluated upon enrollment. The primary measure of effectiveness was a reduction of live mite counts following each treatment.

Skin lesion scoring: The Investigator conducted skin lesion scoring at the time of each scraping. The scoring categories were: alopecia, erythema, papules, pruritus, pyoderma, and scaling/crusts. Each lesion was graded as either absent (0), mild (1), moderate (2), or severe (3).

(7) Statistical Methods:

Percent reduction of mites was calculated as 100 times the ratio of the difference between the geometric mean mite counts at baseline, minus the geometric mean mite count post-treatment, to the geometric mean mite count at baseline.

d. Results:

The investigational product, 10% imidacloprid + 2.5% moxidectin topical solution, provided 98.7% reduction of live mite counts on Study Day 28, and 99.5% reduction in live mite counts on Study Day 56. At the study start, the weighted average of skin lesion scores for the dogs in the treatment group ranged from 1.95 to 2.72. At the Study Day 28 evaluation, the range was 0.31 to 0.92, and on Study Day 56 the range was 0.03 to 0.51.

e. Adverse Reactions:

The following adverse reactions were reported in dogs in the treatment group: hematochezia, diarrhea, vomiting, inappetence, lethargy, and pyoderma.

f. Conclusions:

This field study demonstrated the safety and effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution for the treatment of sarcoptic mange in dogs. Effectiveness, as measured by the reduction in live mite counts, was greater than 90% following one or two monthly administrations.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for the indication of treatment and control of sarcoptic mange cause by *Sarcoptes scabiei* var. *canis.* The FOI Summary for the original approval of NADA 141-251, dated December 20, 2006, contains a summary of target animal safety studies for dogs.

A. Field Safety Study:

1. For the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs:

   a. Title:

      "Clinical Evaluation of the Safety and Efficacy of 10% Imidacloprid + 2.5% Moxidectin Topical Solution for the Treatment of *Dirofilaria immitis* Circulating Microfilariae in Dogs" (Study Number: 152.260)

   b. Investigators:

      Lynn Buzhardt, DVM
      Zachary, LA

      Bill Campaigne, DVM
      Seguin, TX

      Richard Mauldin, DVM
      Oklahoma City, OK

      Ken McMillan, DVM
      Pell City, AL

      Roger Sifferman, DVM
      Springfield, MO

      David H. Wright, DVM
      Collierville, TN

   c. Study Design:

      (1) Objective:

         To evaluate the safety and effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution administered at the label dose of 0.1 mL/kg (0.045 mL/lb), for the treatment of circulating *D. immitis* microfilariae in heartworm-positive dogs, when used alone or in combination with melarsomine dihydrochloride under clinical conditions of use.

      (2) Study Animals:

         214 purebred or mixed breed (110 male and 104 female) dogs, 6 months to 12 years of age, weighing 3.0 to 139.7 lbs.

      (3) Treatment Groups:

         Group 1: 10% imidacloprid + 2.5% moxidectin topical solution on Study Days 0 and 28
         Group 2: 10% imidacloprid + 2.5% moxidectin topical solution on Study Days 0 and 28 and melarsomine dihydrochloride on Study Days -14, 14, and 15.

(4) Dose and Route of Administration:

The 10% imidacloprid + 2.5% moxidectin topical solution was applied topically between the shoulder blades on Study Days 0 and 28 at 0.1 mL/kg (0.045 mL/lb) bodyweight. Melarsomine dihydrochloride was administered at 2.42 mg/kg (1.1 mg/lb) by deep muscular injection in the epaxial (lumbar) muscles per label dosing recommendations for dogs with Heartworm Disease Classification 3 on Study Days -14, 14, and 15.

(5) Measurements and Observations:

An antigen test was conducted to determine heartworm infection on Study Day -14. The modified Knott's test was conducted to establish pre-treatment microfilariae counts, and again on Study Days 14, 28, and 42 (study end). A physical examination, blood and urine analyses, and chest radiographs were conducted prior to or on Day -14, and a physical examination was conducted at the end of the study (Study Day 42). Dogs were observed in the clinic for adverse events at 2, 4, 8, and 12 hrs post-treatment on Study Days -14, 0, 14, 15, and 28. Dogs were observed by their owners at home during the remainder of the study.

(6) Statistical Methods:

(a) Effectiveness:

Microfilaria counts from both treatment groups were combined and log transformed prior to inferential analyses. Effectiveness of 10% imidacloprid + 2.5% moxidectin topical solution was demonstrated if the percent reduction of microfilariae on Study Day 42 in the combined treatment groups was >90% and there was a statistically significant difference between the pre- and post-treatment log microfilariae counts.

(b) Safety:

Safety variables, including post-treatment observations by the Investigator and owner, were descriptively summarized by treatment group.

d. Results:

A total of 181 dogs were evaluated for effectiveness. Each dog was antigen and microfilaria positive for *D. immitis* prior to Study Day -14. The post-treatment circulating microfilaria counts on Study Day 28 and 42 were significantly reduced compared to the pre-treatment counts ($p < 0.0001$) with effectiveness of 99.3% on Study Day 28, and 99.5% on Study Day 42. The results are summarized in Table 3 below.

Table 3: Summary of Effectiveness Against Circulating Microfilariae (Treatment Groups Combined)

Parameter	Pre-Treatment Values	Study Day 28 Values	Study Day 42 Values
Number of dogs	181	178	181
Geometric Mean	4480.9	32.5	21.8
% Effectiveness	-	99.3	99.5
p-value	-	<0.0001	<0.0001

The number of circulating microfilariae was reduced in the study population overall; however, not all dogs treated with 10% imidacloprid + 2.5% moxidectin topical solution had microfilariae counts reduced to zero. The microfilarial count in some heartworm-positive dogs increased or remained unchanged following treatment with 10% imidacloprid + 2.5% moxidectin topical solution alone or with melarsomine dihydrochloride. Effectiveness against circulating *D. immitis* microfilariae was > 90% at five of six sites; however, one site had effectiveness of 73.3%.

e. Adverse Reactions:

There were 214 dogs evaluated for safety: 106 dogs administered 10% imidacloprid + 2.5% moxidectin topical solution alone, and 108 dogs administered 10% imidacloprid + 2.5% moxidectin topical solution and melarsomine dihydrochloride.

The adverse reactions observed following treatment with 10% imidacloprid + 2.5% moxidectin topical solution alone or in a dosing regimen with melarsomine dihydrochloride are shown in Table 4.

Table 4: Adverse Reactions

Adverse Reaction	Dogs Treated With 10% Imidacloprid + 2.5% Moxidectin Topical Solution Only (n=106)	Dogs Treated With 10% Imidacloprid + 2.5% Moxidectin Topical Solution + Melarsomine Group (n=108)
Cough	24 (22.6%)	25 (23.1%)
Lethargy	14 (13.2%)	42 (38.9%)
Vomiting	11 (10.4%)	18 (16.7%)
Diarrhea, including hemorrhagic	10 (9.4%)	22 (20.4%)
Inappetance	7 (6.6%)	19 (17.6%)
Dyspnea	6 (5.7%)	10 (9.3%)
Tachypnea	1 (<1%)	7 (6.5%)
Pulmonary hemorrhage	0	1 (<1%)
Death	0	3 (2.8%)

Three dogs treated with 10% imidacloprid + 2.5% moxidectin topical solution in a dosing regimen with melarsomine dihydrochloride died of pulmonary embolism from dead and dying heartworms. One dog treated with 10% imidacloprid + 2.5% moxidectin topical solution and melarsomine dihydrochloride experienced pulmonary hemorrhage and responded to supportive medical treatment. Following the first treatment with 10% imidacloprid + 2.5% moxidectin topical solution only, two dogs experienced adverse reactions (coughing, vomiting, and dyspnea) that required hospitalization. In both groups, there were more adverse reactions to 10% imidacloprid + 2.5% moxidectin topical solution following the first treatment than the second treatment.

f. Conclusions:

The 10% imidacloprid + 2.5% moxidectin topical solution was well-tolerated when administered to heartworm-positive dogs, alone or when used in a dosing regimen with melarsomine dihydrochloride adulticide treatment. ADVANTAGE MULTI for Dogs was effective for the treatment of circulating *D. immitis* microfilariae in heartworm-positive dogs.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ADVANTAGE MULTI for Dogs:

"Not for human use. Keep out of the reach of children. Children should not come in contact with application sites for two (2) hours after application. Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. Exposure to the product has been reported to cause headache; dizziness; and redness, burning, tingling, or numbness of the skin. Wash hands thoroughly with soap and warm water after handling.

If contact with eyes occurs hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops of persists, contact a physician. If swallowed, call poison control center or physician 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 physician. People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. 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 Material Safety Data Sheet (MSDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826."

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that ADVANTAGE MULTI for Dogs, when used according to the label, is safe and effective for the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs and for the treatment and control of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*.

A. Marketing Status:

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 *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs and sarcoptic mange caused by *Sarcoptes scabiei* var. *canis*, and to monitor the safe use of the product.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs

and the treatment and control of sarcoptic mange cause by *Sarcoptes scabiei* var. *canis* for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.