Date of Approval: January 19, 2007

FREEDOM OF INFORMATION SUMMARY

NADA 141-254

ADVANTAGE MULTI for Cats

Imidacloprid + Moxidectin

ADVANTAGE MULTI for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. ADVANTAGE MULTI for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. ADVANTAGE MULTI for Cats is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the following intestinal parasites:

Intestinal Parasite		**Intestinal Stage**		
		Adult	**Immature Adult**	**Fourth Stage Larvae**
Hookworm Species	*Ancylostoma tubaeforme*	X	X	X
Roundworm Species	*Toxocara cati*	X		X

Sponsored by:
Bayer HealthCare LLC
Animal Health Division

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1. GENERAL INFORMATION:

a. File Number: NADA 141-254

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

Drug Labeler Code: 000859

c. Established Name: imidacloprid + moxidectin

d. Proprietary Name: ADVANTAGE MULTI for Cats

e. Dosage Form: Solution

f. How Supplied: Unit applicator tube
Applicator tube size and applications per package:
3 x 0.23 mL tubes
6 x 0.4 mL tubes
6 x 0.8 mL tubes

g. How Dispensed: Rx

h. Amount of Active Ingredients: 10% imidacloprid + 1% moxidectin

i. Route of Administration: Topical

j. Species/Class: Cats

k. Recommended Dosage:
The recommended minimum dose is 4.5 mg/lb (10 mg/kg) imidacloprid and 0.45 mg/lb (1.0 mg/kg) moxidectin, once a month by topical administration, as specified in the following table.

Cat Weight (lb)	ADVANTAGE MULTI For Cats	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2 – 5	ADVANTAGE MULTI 5	0.23	23	2.3
5.1 – 9	ADVANTAGE MULTI 9	0.4	40	4
9.1 – 18 *	ADVANTAGE MULTI 18	0.8	80	8

*Cats over 18 lbs should be treated with the appropriate combination of ADVANTAGE MULTI For Cats tubes.

l. Pharmacological Category: Antiparasitic

m. Indications:

ADVANTAGE MULTI for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis.* ADVANTAGE MULTI for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. ADVANTAGE MULTI for Cats is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the following intestinal parasites:

Intestinal Parasites		**Intestinal Stage**		
		Adult	**Immature Adult**	**Fourth Stage Larvae**
Hookworm Species	*Ancylostoma tubaeforme*	X	X	X
Roundworm Species	*Toxocara cati*	X		X

2. EFFECTIVENESS:

a. Dosage Characterization for the Treatment of Flea Infestations:

The dose of 10 mg/kg topical imidacloprid was developed for the Environmental Protection Agency (EPA)-registered product ADVANTAGE. The results of two studies using 10% imidacloprid that support the selection of the 10 mg/kg label dose of imidacloprid to kill adult fleas on cats are summarized in the following table. The bolded doses were less than 90% effective.

Table 1: Summary of Dosage Characterization Studies for Fleas

Report #	**Location**	**Imidacloprid dose (mg/kg)**	**# of cats**	**% Effectiveness**				
				Day 1	**Day 7**	**Day 14**	**Day 21**	**Day 28**
74571	Greenbrier, Arkansas	**3.75**	5	100	92.0	**79.6**	**54.0**	**53.9**
		7.5	5	100	97.2	94.0	**67.8**	**56.5**
74634	Queensland, Australia	10	10	99.5	99.1	96.9	96.2	95.7

b. Substantial Evidence of Effectiveness for the Treatment of Flea Infestations:

1) Evaluation of the Effectiveness of Imidacloprid + Moxidectin for the Control of Fleas on Cats (Study #151.035, Report #75251)

Purpose: The objective of this investigation was to evaluate the safety, and initial and residual flea (*Ctenocephalides felis*) control effectiveness of topically applied imidacloprid + moxidectin on cats.

Investigator: David R. Young, DVM, PhD

Location: Young Veterinary Research Services, Turlock, CA

Animals: 16 mixed breed cats (8 males and 8 females), all adults, between 5.7 and 11.2 pounds, 8 cats per treatment group

Treatment Groups: Group 1: 10% Imidacloprid + 1.0% Moxidectin
Group 2: Control (vehicle without active ingredients)

Treatment Dosages: ≤ 9 lbs 0.4 mL
> 9 lbs 0.8 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 50 days (including acclimation)

Study Design: Each cat was infested with 100 adult fleas on Study Day -5. Fleas were counted and removed on Day -4. Cats were assigned to treatment groups based on the Day -4 flea counts. Cats were treated once on Day 0. Each cat was infested with 100 adult fleas on Days -1, 6, 13, 20, 27, and 34.

Variables Measured: Cats were combed and live fleas were counted and removed on Days 1, 7, 14, 21, 28, and 35. Cats were observed for adverse reactions at 1, 2, 3, 4, 6, 8, and 12 hours post-treatment and daily thereafter.

Results: Percent effectiveness against flea infestations and the geometric mean number of fleas per cat are shown in the table below:

Table 2: Percent Flea Effectiveness and Geometric Mean Number of Fleas

Day	Group 1: Imidacloprid/Moxidectin		Group 2: Control
	Percent Flea Effectiveness	Geometric mean # of fleas	Geometric mean # of fleas
1	100	0.0	47.5
7	98.9	0.3	27.7
14	98.9	0.8	79.8
21	97.3	2.0	74.9
28	97.9	1.7	83.5
35	89.8	8.0	78.3

Adverse Reactions: No adverse reactions were reported.

Conclusions: The effectiveness of a single topical dose of imidacloprid + moxidectin against *Ctenocephalides felis* ranged from 97.3% to 100% for Day 1 through Day 28.

2) Evaluation of the Effectiveness of Imidacloprid + Moxidectin against Flea Infestations on Cats (Study #141.522, Report #75413)

Purpose: The objectives of this investigation were: 1) to evaluate the safety, and initial and residual flea (*Ctenocephalides felis*) control effectiveness of topically applied imidacloprid + moxidectin on cats and 2) to demonstrate that moxidectin alone is not effective against fleas and that moxidectin does not interfere with the insecticidal activity of imidacloprid against fleas in the combined formulation.

Investigator: Dr. Olaf Hansen

Location: Bayer AG, Leverkusen, Germany

Animals: 32 European short hair breed (16 males and 16 females), all adults, between 7.2 and 17.0 pounds, 8 cats per treatment group

Treatment Groups: Group 1: 10% Imidacloprid
Group 2: 10% Imidacloprid + 1.0% Moxidectin
Group 3: 1.0% Moxidectin
Group 4: Control (vehicle without active ingredients)

Treatment Dosages: $\leq$ 9 lbs 0.4 mL
> 9 lbs 0.8 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 50 days (including acclimation)

Study Design: Each cat was infested with 100 adult fleas on Study Day -5. Fleas were counted and removed on Day -4. Cats were assigned to treatment groups based on the Day -4 flea counts. The cats were infested with 100 adult fleas on Days -1, 6, 13, 20, 27, and 34.

Variables Measured: Each cat was combed, and live fleas counted and removed on Days 1, 7, 14, 21, 28, and 35. Cats were observed for adverse reactions at 1, 2, 3, 4, 6, 8, and 12 hours post-treatment and daily thereafter.

Results: Percent effectiveness against flea infestations and the geometric mean number of fleas per cat are shown in the table below:

Table 3: Percent Flea Effectiveness and Geometric Mean Number of Fleas

Day	**Group 1 Imidacloprid**		**Group 2 Imidacloprid/Moxidectin**		**Group 3 Moxidectin**		**Group 4 Control**
	Percent Effectiveness	Flea Count*	Percent Effectiveness	Flea Count	Percent Effectiveness	Flea Count	Flea Count
1	98.4	0.2	100	0.0	N/A	14.2	11.9
7	100	0.0	98.7	0.2	2.9	14.0	14.4
14	100	0.0	100	0.0	42.9	12.3	21.6
21	100	0.0	89.4	2.8	35.5	16.8	26.0
28	98.6	0.3	98.0	0.5	52.7	10.9	23.0
35	96.5	1.1	88.4	3.7	55.4	14.2	31.7

*All flea counts are geometric means

Adverse Reactions: No adverse reactions were reported.

Conclusions: The effectiveness of a single topical dose of imidacloprid + moxidectin against *Ctenocephalides felis* ranged from 89.4% to 100% for Day 1 through Day 28. The combining of moxidectin with imidacloprid did not interfere with the effectiveness of imidacloprid against adult fleas. Moxidectin alone provided limited flea effectiveness.

c. Dosage Characterization for the Prevention of Heartworm Disease:
Refer to section 2.e., Dosage Characterization for the Treatment and Control of Intestinal Nematodes, which establishes a minimum effective dose for moxidectin.

d. Substantial Evidence for the Prevention of Heartworm Disease:

1) Evaluation of the Effectiveness of a Topically Applied Combination of Imidacloprid and Moxidectin for the Prevention of Heartworm Disease in Cats (Study #150.867, Report #75319)

Purpose: The objectives of this investigation were 1) to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin against experimentally induced larval heartworm (*Dirofilaria immitis*) infection in cats and 2) to confirm that imidacloprid alone is not effective against larval stages of *D. immitis* and that imidacloprid does not interfere with the activity of moxidectin against *D. immitis* in the combined formulation.

Investigator: John McCall, PhD

Location: TRS Labs Inc., Athens, GA

Animals: 40 mixed breed cats (20 males and 20 females), 5 to 8 months of age, between 5.0 and 9.7 pounds, 10 cats per treatment group

Treatment Groups: Group 1: 10% Imidacloprid + 1.0% Moxidectin
Group 2: 1.0% Moxidectin
Group 3: 10% Imidacloprid
Group 4: Control (vehicle without active ingredients)

Treatment Dosages: ≤ 9 lbs 0.4 mL
> 9 lbs 0.8 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 171 days

Study Design: Each cat was experimentally infected subcutaneously with 100 stage L3 heartworm larvae (*Dirofilaria immitis*) on Study Day -30. Cats were randomly assigned to treatment groups prior to treatment on Day 0. Following a 140-day post-treatment observation period, cats were humanely euthanized and necropsied.

Variables Measured: Cats were observed for any adverse reactions at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-treatment and daily thereafter. Adult heartworm antigen tests were performed prior to Day -30 and on Day 90 to rule out a natural infection acquired

prior to the study. At necropsy on Day 139, adult heartworms were recovered from the cardiovascular system, thoracic cavity, and/or abdominal cavity and counted.

Results: No adult heartworms (*D. immitis*) were recovered at necropsy from cats treated with moxidectin (Groups 1 and 2). Cats in Groups 3 and 4 had geometric means of 4.0 and 3.2 adult heartworms per cat, respectively. See Table 4:

Table 4: Effectiveness Against the Development of Adult Heartworms

Group	**Treatment**	**# of Cats with *D. immitis***	**Geometric Mean # of *D. immitis***	**Percent Effectiveness**
1	Imidacloprid + Moxidectin	0/10	0.0	100
2	Moxidectin	0/10	0.0	100
3	Imidacloprid	7/10	4.0	NA*
4	Control	6/10	3.2	NA

*Not applicable

Adverse Reactions: No adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective in preventing experimentally induced heartworm disease in cats caused by *Dirofilaria immitis*. Imidacloprid alone demonstrated no activity against *D. immitis*. The effectiveness of moxidectin was not diminished by its combination with imidacloprid.

2) Evaluation of the Efficacy of a Topically Applied Combination of Imidacloprid and Moxidectin for the Prevention of Heartworm Disease in Cats (Study #151.242, Report #75370)

Purpose: The objective of this investigation was to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin against experimentally induced larval heartworm (*Dirofilaria immitis*) infection in cats.

Investigator: Dwight D. Bowman, PhD

Location: Cheri-Hills Kennel, Stanwood, MI

Animals: 20 mixed breed cats (11 males and 9 females), 5.5 to 6.5 months of age, between 3.8 and 8.7 pounds, 10 cats per treatment group

Treatment Groups: Group 1: 10% Imidacloprid + 1.0% Moxidectin
Group 2: Control (vehicle without active ingredients)

Treatment Dosage: ≤ 9 lbs 0.4 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 171 days

Study Design: Each cat was experimentally infected subcutaneously with 100 stage L3 heartworm larvae (*Dirofilaria immitis*) on Study Day -30. Cats were randomly assigned to treatment groups prior to treatment on Day 0. Following a 140-day post-treatment observation period, cats were humanely euthanized and necropsied.

Variables Measured: Cats were observed for any adverse reactions at 1, 2, 3, 4, 6, 8, 12 and 24 hours post-treatment and daily thereafter. Adult heartworm antigen tests were performed prior to Day -30 and on Day 90 to rule out a natural infection acquired prior to the study. At necropsy on Day 139, adult heartworms were recovered from the cardiovascular system, thoracic cavity, and/or abdominal cavity and counted.

Results: No adult heartworms (*D. immitis*) were recovered at necropsy from cats treated with imidacloprid + moxidectin. Cats in the control group had a geometric mean of 2.2 adult heartworms per cat. See Table 5:

Table 5: Effectiveness against the Development of Adult Heartworms

Group	**Treatment**	**# of Cats with *D. immitis***	**Geometric Mean # of *D. immitis***	**Percent Effectiveness**
1	Imidacloprid + Moxidectin	0/10	0.0	100
2	Control	8/10	2.2	NA

Adverse Reactions: Following treatment, a few cats in each group displayed signs of salivation, facial pawing, and head shaking. All cats returned to normal within minutes. No other reactions were observed in any cats for the duration of the study.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective in preventing experimentally induced heartworm disease in cats caused by *Dirofilaria immitis*.

e. Dosage Characterization for the Treatment and Control of Intestinal Nematodes: Four dosage characterization studies were conducted in Queensland, Australia, against adult *Toxocara* spp. and *Ancylostoma* spp. natural infections in cats, using different concentrations of moxidectin combined with 10% imidacloprid. The dosage volume was fixed at 0.1 mL/kg (0.45 mL/lb) to maintain the same dosage schedule established for ADVANTAGE. The results of the dosage characterization studies are summarized in Table 6. The data indicate that *Toxocara* spp. is the dose-limiting parasite. The

data show that moxidectin at a dose of 1.0 mg/kg was greater than 90% effective against *Toxocara* spp. The bolded dose was less than 90% effective.

Table 6: Summary of Dosage Characterization Studies for Intestinal Nematodes

Study #	Parasite	Moxidectin dose (mg/kg)	Percent Effectiveness	# of cats
75428	*Ancylostoma* spp.	2.5	100	6
	Toxocara spp.	2.5	100	5
75429	*Toxocara* spp.	1.75	99.4	7
75430	*Toxocara* spp.	1.0	98.4	8
		0.25	**72.6**	9
75431	*Ancylostoma* spp.	1.0	100	8

f. Substantial Evidence for the Treatment and Control of Adult Intestinal Nematodes:

1) Evaluation of the Effectiveness of a Combination of Imidacloprid and Moxidectin against Natural Infections with *Toxocara cati* in Cats (Study #150.975, Report # 75306)

Purpose: The objectives of this investigation were 1) to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with adult *Toxocara cati* in cats and 2) to confirm that imidacloprid alone is not effective against *T. cati* and that imidacloprid does not interfere with the activity of moxidectin against *T. cati* in the combined formulation.

Investigator: William Barton, PhD

Location: Central Arizona Veterinary Laboratory, Amarillo, TX

Animals: 32 mixed breed cats (15 males and 17 females), 6 to 48 months of age, between 3.5 and 13.8 pounds, 8 cats per treatment group

Treatment Groups: Group 1: 10% Imidacloprid + 1.0% Moxidectin
Group 2: 1.0% Moxidectin
Group 3: Control (vehicle without active ingredients)
Group 4: 10% Imidacloprid

Treatment Dosages: ≤ 9 lbs 0.4 mL
> 9 lbs 0.8 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Replicates (4): 18 to 22 days (including acclimation)

Study Design: Cats naturally infected with adult *Toxocara cati* were randomly assigned to treatment groups based on pre-treatment *T. cati* egg counts. Following a 10 day post-treatment observation period, cats were humanely euthanized and necropsied.

Variables Measured: Cats were observed for any adverse reactions at 1, 2, 4, and 8 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on adult *T. cati* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against adult *Toxocara cati* in cats is shown in Table 7:

Table 7: Effectiveness of Imidacloprid + Moxidectin against Adult *Toxocara cati*

Group	**Treatment**	**# of Cats with *T. cati***	**Geometric Mean # of Adult *T. cati***	**Percent Effectiveness**
1	Imidacloprid + Moxidectin	0/8	0.0	100
2	Moxidectin	0/7	0.0	100
3	Control	5/8	2.5	NA
4	Imidacloprid	7/8	5.1	NA

Adverse Reactions: One cat from Group 2 died seven days after treatment. The cat was coughing on Day 4, had bloody diarrhea on Day 5, and was depressed and unsteady on Day 6. This cat was thin and had lost weight during the week prior to moxidectin treatment. Post mortem examination conducted at an independent diagnostic laboratory reported lesions compatible with feline panleukopenia. One cat from Group 1 developed a raw area on its back and ocular discharge after treatment with imidacloprid + moxidectin. During both the pre- and post-treatment periods, occasional observations of loose stools, depression, or ocular discharge were observed in cats from all four treatment groups.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective against natural infections with adult *Toxocara cati* in cats. Imidacloprid alone was not effective against *T. cati*. The anthelmintic activity of moxidectin was not diminished by its combination with imidacloprid.

2) Evaluation of the Effectiveness of a Combination of Imidacloprid and Moxidectin against Natural Infections with *Toxocara cati* in Cats (Study #151.250, Report #75368)

Purpose: The objectives of this investigation were 1) to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with adult *Toxocara cati* in cats and 2) to confirm that imidacloprid alone is not effective against *T. cati* and that imidacloprid does not interfere with the activity of moxidectin against *T. cati* in the combined formulation.

Investigator: Larry Cruthers, PhD

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

Animals: 32 various breed cats (13 males and 19 females), 3 to 48 months of age, between 4.0 and 12.8 pounds, 7 to 9 cats per treatment group

Treatment Groups: Group 1: Control (vehicle without active ingredients)
Group 2: 10% Imidacloprid + 1.0% Moxidectin
Group 3: 1.0% Moxidectin
Group 4: 10% Imidacloprid

Treatment Dosages: ≤ 9 lbs 0.4 mL
> 9 lbs 0.8 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Replicates (5): 18 days (including acclimation)

Study Design: Cats naturally infected with adult *Toxocara cati* were randomly assigned to treatment groups based on pre-treatment *T. cati* egg counts. Following a 10 day post-treatment observation period, cats were humanely euthanized and necropsied.

Variables Measured: Cats were observed for any adverse reactions at 1, 2, 4, and 8 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on adult *T. cati* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against adult *Toxocara cati* in cats is shown in Table 8:

Table 8: Effectiveness of Imidacloprid + Moxidectin against Adult *Toxocara cati*

Group	Treatment	# of Cats with *T. cati*	Geometric Mean # of Adult *T. cati*	Percent Effectiveness
1	Control	8/8	4.3	NA
2	Imidacloprid + Moxidectin	0/6	0.0	100
3	Moxidectin	0/8	0.0	100
4	Imidacloprid	9/9	5.7	NA

Adverse Reactions: One cat from Group 2 became ill within 1 hour after treatment with imidacloprid + moxidectin. At 1 hour post-treatment the cat had vomited and had loose stool and nasal discharge; at 2 hours post-treatment it was also depressed; at 4 hours post-treatment the cat was unsteady and had a rapid respiratory rate; and at 8 hours post-treatment it was febrile and dehydrated. In spite of veterinary care, this cat died the day following treatment with imidacloprid + moxidectin. Evaluation of tissues by an independent diagnostic laboratory did not determine the cause of death. This cat was thin and had lost weight during the week prior to imidacloprid + moxidectin treatment. Another cat from Group 2 developed ocular and nasal discharge, slow and difficult breathing, depression, anorexia, unsteadiness, a fever and dehydration 3 days following treatment with imidacloprid + moxidectin. Veterinary care was initiated, but respiratory congestion continued until the end of the study. During the pre-treatment period, upper respiratory signs and conjunctivitis were observed in 3 cats that improved prior to random placement into the imidacloprid (Group 4) treatment group. During the pre- and post-treatment periods, loose stools or diarrhea were occasionally observed in cats from all four treatment groups.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective against natural infections with adult *Toxocara cati* in cats. Imidacloprid alone was not effective against *T. cati*. The anthelmintic activity of moxidectin was not diminished by its combination with imidacloprid.

3) Evaluation of the Effectiveness of a Combination of Imidacloprid and Moxidectin Against Adult *Ancylostoma tubaeforme* in Cats (Study #151.390, Report #75393)

Purpose: The objective of this investigation was to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with adult *Ancylostoma tubaeforme* in cats.

Investigator: Craig R. Reinemeyer, DVM, PhD

Location: East Tennessee Clinical Research, Inc., Knoxville, TN

Animals: 20 domestic short hair breed cats (10 males and 10 females), approximately 3 months of age, between 1.5 and 2.5 pounds, 10 cats per treatment group

Treatment Groups: Group 1: Control (vehicle without active ingredients)
Group 2: 10% Imidacloprid + 1.0% Moxidectin

Treatment Dosages: ≤ 9 lbs 0.4 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 39 days (including acclimation)

Study Design: Each cat was experimentally infected by oral administration of 300 stage L3 *Ancylostoma tubaeforme* larvae on Study Day 0. Cats were randomly assigned to treatment groups based on pre-treatment *A. tubaeforme* fecal egg counts. Cats were treated on Day 21 and humanely euthanized and necropsied on Day 31.

Variables Measured: Cats were observed for any adverse reactions at 0.5, 1, 2, 4, and 8 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on adult *A. tubaeforme* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against adult *Ancylostoma tubaeforme* in cats is shown in Table 9:

Table 9: Effectiveness of Imidacloprid + Moxidectin against Adult *A. tubaeforme*

Group	**Treatment**	**# of Cats with *A. tubaeforme***	**Geometric Mean # of Adult *A. tubaeforme***	**Percent Effectiveness**
1	Control	10/10	16.9	NA
2	Imidacloprid + Moxidectin	0/10	0.0	100

Adverse Reactions: No adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective against experimental infections with *Ancylostoma tubaeforme* in cats.

4) Evaluation of the Effectiveness of a Combination of Imidacloprid and Moxidectin Against Natural Infections of *Ancylostoma tubaeforme* in Cats (Study #151.282, Report #75394)

Purpose: The objective of this investigation was to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with adult *Ancylostoma tubaeforme* in cats.

Investigator: Larry R. Cruthers, PhD

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

Animals: 16 domestic short and long-hair breed cats (7 males and 9 females), 1 to 6.5 years of age, between 5.4 and 10 pounds, 8 cats per treatment group

Treatment Groups: Group1: Control (vehicle without active ingredients)
Group 2: 10% Imidacloprid + 1.0% Moxidectin

Treatment Dosages: ≤ 9 lbs 0.4 mL
> 9 lbs 0.8 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Replicates (4): 18 – 20 days (including acclimation)

Study Design: Cats naturally infected with adult *Ancylostoma tubaeforme* were randomly assigned to treatment groups based on pre-treatment *A. tubaeforme* egg counts. Following a 10 day post-treatment observation period, cats were humanely euthanized and necropsied.

Variables Measured: Cats were observed for any adverse reactions at 0.5, 1, 2, 4, and 8 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on adult *A. tubaeforme* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against adult *Ancylostoma tubaeforme* in cats is shown in Table 10.

Table 10: Effectiveness of Imidacloprid + Moxidectin against Adult *A. tubaeforme*

Group	**Treatment**	**# of Cats with *A. tubaeforme***	**Geometric Mean # of Adult *A. tubaeforme***	**Percent Effectiveness**
1	Control	8/8	7.3	NA
2	Imidacloprid + Moxidectin	1/8	0.1	98.8

Adverse Reactions: No adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 98.8% effective against natural infections with *Ancylostoma tubaeforme* in cats.

g. Substantial Evidence for the Treatment and Control of Immature Intestinal Nematodes:

1) Evaluation of the Effectiveness of a combination of Imidacloprid and Moxidectin Against Immature (Fourth Stage Larvae) *Toxocara cati* in Cats (Study #141.123, Report #75410)

Purpose: The objective of this investigation was to confirm the safety and efficacy of topically applied imidacloprid + moxidectin as a treatment for infections with the fourth stage larvae of *Toxocara cati* in cats.

Investigator: Dara Cooke, BSc

Location: Biological Laboratories Europe LTD., Ballina, Ireland

Animals: 32 domestic short hair breed cats (16 males and 16 females), 2.5 to 3.2 months old, between 3.0 and 5.8 pounds at treatment, 8 cats per treatment group.

Treatment Groups: Group 1: Control (vehicle without active ingredients)
Group 2: 10% Imidacloprid + 1.0% Moxidectin
Group 3: 10% Imidacloprid + 1.0% Moxidectin
Group 4: Control (vehicle without active ingredients)

Treatment Dosages: ≤ 9 lbs 0.4 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 37 days (including acclimation)

Study Design: Cats were randomly assigned to groups. Each cat was artificially infected by oral administration of approximately 300 infective *Toxocara cati* ova on Study Day 0. Cats in Groups 1 and 2 were treated 14 days following infection and necropsied 19 days following infection. Cats in Groups 3 and 4 were treated 24 days following infection and necropsied 29 days following infection.

Variables Measured: Cats were observed for any adverse reactions at 10 minutes and at 1, 3, and 6 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on *T. cati* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against fourth stage larvae of *T. cati* in cats is shown in Table 11:

Table 11: Effectiveness of Imidacloprid + Moxidectin against 4th Stage Larvae *T. cati*

Group	Treatment	# of Cats with *T. cati* 4th Stage Larvae	Geometric Mean # of *T. cati* 4th Stage Larvae	Percent Effectiveness
1	Control, Day 14 dose	7/8	5.8	NA
2	Imidacloprid + Moxidectin, Day 14 dose	0/8	0.0	100
3	Imidacloprid + Moxidectin, Day 24 dose	1/8	0.3	95.9
4	Control, Day 24 dose	7/8	6.7	NA

Adverse Reactions: One control (vehicle) cat had hypersalivation at the 10 minute observation time. No other adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 95.9 to 100% effective against the L4 stage of *Toxocara cati* in experimentally infected cats.

2) Evaluation of the Effectiveness of a combination of Imidacloprid and Moxidectin Against Immature (Fourth Stage Larvae) *Toxocara cati* in Cats (Study #151.159, Report #75318)

Purpose: The objective of this investigation was to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with the fourth stage larvae of *Toxocara cati* in cats.

Investigator: Craig R. Reinemeyer, DVM, PhD

Location: East Tennessee Clinical Research, Knoxville, TN

Animals: 32 domestic short hair breed cats (16 males and 16 females), approximately 2 to 3 months old, between 2.2 and 4.6 pounds at treatment, 8 cats per treatment group

Treatment Groups: Group 1: 10% Imidacloprid + 1.0% Moxidectin
Group 2: Control (vehicle without active ingredients)
Group 3: Control (vehicle without active ingredients)
Group 4: 10% Imidacloprid + 1.0% Moxidectin

Treatment Dosages: ≤ 9 lbs 0.4 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 37 days (including acclimation)

Study Design: Cats were randomly assigned to groups. Each cat was artificially infected by oral administration of approximately 500 infective *Toxocara cati* ova on Study Day 0. Cats in Groups 1 and 2 were treated 14 days following infection and necropsied 19 days following infection. Cats in Groups 3 and 4 were treated 24 days following infection and necropsied 29 days following infection.

Variables Measured: Cats were observed for any adverse reactions at 0.5, 1, 2, 4, and 8 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on *T. cati* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against fourth stage larvae of *T. cati* in cats is shown in Table 12:

Table 12: Effectiveness of Imidacloprid + Moxidectin against 4th Stage Larvae *T. cati*

Group	Treatment	# of Cats with *T. cati* 4th Stage Larvae	Geometric Mean # of *T. cati* 4th Stage Larvae	Percent Effectiveness
1	Imidacloprid + Moxidectin, Day 14 dose	3/8	0.5	98.6
2	Control, Day 14 dose	8/8	31.6	NA
3	Control, Day 24 dose	8/8	9.0	NA
4	Imidacloprid + Moxidectin, Day 24 dose	1/8	0.1	99.0

Adverse Reactions: No adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 98.6 to 99.0% effective against the L4 stage of *Toxocara cati* in experimentally infected cats.

3) Evaluation of the Effectiveness of a combination of Imidacloprid and Moxidectin Against Immature (Fourth Stage Larvae and Immature Adults) *Ancylostoma tubaeforme* in Cats (Study #141.319, Report #75409)

Purpose: The objective of this investigation was to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with larval and immature adult stages of *Ancylostoma tubaeforme* in cats.

Investigator: Dara Cooke, BSc

Location: Biological Laboratories Europe LTD., Ballina, Ireland

Animals: 32 domestic short hair breed cats (16 males and 16 females), 2.8 to 3.9 months old, between 3.1 and 5.3 pounds at treatment, 8 cats per treatment group

Treatment Groups: Group 1: Control (vehicle without active ingredients)
Group 2: 10% Imidacloprid + 1.0% Moxidectin
Group 3: 10% Imidacloprid + 1.0% Moxidectin
Group 4: Control (vehicle without active ingredients)

Treatment Dosages: ≤ 9 lbs 0.4 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 24 days (including acclimation)

Study Design: Cats were randomly assigned to groups. Each cat was artificially infected by oral administration of approximately 300 infective *Ancylostoma tubaeforme* larvae on Study Day 0. Cats in Groups 1 and 2 were treated 7 days following infection and necropsied 12 days following infection. Cats in Groups 3 and 4 were treated 11 days following infection and necropsied 16 days following infection.

Variables Measured: Cats were observed for any adverse reactions at 10 minutes and at 1, 3, and 6 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on *A. tubaeforme* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against immature *A. tubaeforme* in cats is shown in Table 13:

Table 13: Effectiveness of Imidacloprid + Moxidectin against immature *A. tubaeforme*

Group	Treatment	*A. tubaeforme* 4th Stage Larvae		*A. tubaeforme* Immature Adults	
		Geometric Mean #	**Percent Effectiveness**	**Geometric Mean #**	**Percent Effectiveness**
1	Control, Day 7 dose	36.3	NA	3.0	NA
2	Imidacloprid + Moxidectin, Day 7 dose	0.0	100	0.0	100
3	Imidacloprid + Moxidectin, Day 11 dose	0.0	100	0.0	100
4	Control, Day 11 dose	45.9	NA	5.0	NA

Adverse Reactions: No adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective against L4 and immature adult stages of *Ancylostoma tubaeforme* in experimentally infected cats.

4) Evaluation of the Effectiveness of a combination of Imidacloprid and Moxidectin Against Immature (Fourth Stage Larvae and Immature Adults) *Ancylostoma tubaeforme* in Cats (Study #151.014, Report #75311)

Purpose: The objective of this investigation was to confirm the safety and effectiveness of topically applied imidacloprid + moxidectin as a treatment for infections with larval and immature adult stages of *Ancylostoma tubaeforme* in cats.

Investigator: Larry Cruthers, PhD

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

Animals: 32 domestic short hair breed cats (21 males and 11 females), 3 to 4 months old, between 3.0 and 5.4 pounds at treatment, 8 cats per treatment group

Treatment Groups: Group 1: Control (vehicle without active ingredients)
Group 2: 10% Imidacloprid + 1.0% Moxidectin
Group 3: Control (vehicle without active ingredients)
Group 4: 10% Imidacloprid + 1.0% Moxidectin

Treatment Dosages: ≤ 9 lbs 0.4 mL

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment

Duration of Study: 26 days (including acclimation)

Study Design: Cats were randomly assigned to groups. Each cat was artificially infected by oral administration of approximately 300 infective *Ancylostoma tubaeforme* larvae on Study Day 0. Cats in Groups 1 and 2 were treated 7 days following infection and necropsied 12 days following infection. Cats in Groups 3 and 4 were treated 11 days following infection and necropsied 18 days following infection.

Variables Measured: Cats were observed for any adverse reactions at 0.5, 1, 2, 4, and 8 hours post-treatment and daily thereafter. At necropsy, worm counts were performed on *A. tubaeforme* recovered from the gastrointestinal tract.

Results: Effectiveness of imidacloprid + moxidectin against immature *A. tubaeforme* in cats is shown in Table 14:

Table 14: Effectiveness of Imidacloprid + Moxidectin against immature *A. tubaeforme*

		A. tubaeforme **4th Stage Larvae**		***A. tubaeforme*** **Immature Adults**	
Group	**Treatment**	**Geometric Mean #**	**Percent Effectiveness**	**Geometric Mean #**	**Percent Effectiveness**
1	Control, Day 7 dose	58.8	NA	0.0	NA
2	Imidacloprid + Moxidectin, Day 7 dose	0.0	100	0.0	NA
3	Control, Day 11 dose	6.0	NA	37.9	NA
4	Imidacloprid + Moxidectin, Day 11 dose	0.0	100	0.0	100

Adverse Reactions: No adverse reactions were reported.

Conclusions: A single topical dose of imidacloprid + moxidectin was 100% effective against L4 and immature adult stages of *Ancylostoma tubaeforme* in experimentally infected cats.

h. Substantial Evidence for the Treatment and Control of Ear Mite Infestations:

1) Evaluation of the Efficacy of an Imidacloprid (10%) / Moxidectin (1%) Spot-on Against *Otodectes cynotis* in cats (Study #143.753, Report #29815)

Purpose: The objective of this study was to evaluate the efficacy of imidacloprid + moxidectin applied topically once or twice at monthly intervals to cats infested with ear mites (*O. cynotis*).

Investigator: L.J. Fourie, PhD

Location: Clin Vet International (Pty) Ltd., Bloemfontein, South Africa

Animals: 40 domestic adult cats (23 males and 17 females), 10 cats per treatment group

Treatment Groups:

Group 1: 10% imidacloprid + 1.0% moxidectin—one treatment
Group 2: 10% imidacloprid + 1.0% moxidectin—two treatments
Group 3: Control (vehicle without active ingredient)—one treatment
Group 4: Control (vehicle without active ingredient)—two treatments

Treatment Dosage: Minimum labeled dose of 10 mg/kg imidacloprid and 1 mg/kg moxidectin (0.1 mL/kg)

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Single treatment (Groups 1 and 3) or 2 treatments (Groups 2 and 4)

Duration of Study: 67 days

Study Design: Adult cats with various hair coat lengths, infested with *O. cynotis*, were randomly assigned to treatment groups and treated on Day 0. Treatments were repeated on Day 28 for Groups 2 and 4.

Variables Measured: Each cat was observed for the presence or absence of live *O. cynotis* by otoscopic examination on day -7. The cats were sedated for recovery of all remaining mites from the ear canal on test Day 30 or test Day 60.

Statistical Analysis: The mean mite counts in Group 1 were compared to those in Group 3 at Day 30; also, the mean mite counts in Group 2 were compared to those in Group 4 at Day 60. Both comparisons were carried out using the Kruskal-Wallis test.

Results: Ear mite infestations were confirmed in all cats on Day -7. Effectiveness of imidacloprid + moxidectin against adult *O. cynotis* in cats is shown in Table 15. There were significantly fewer mites in the treated group (imidacloprid + moxidectin) compared to the placebo group, both at Day 30 ($p = 0.0002$) and at Day 60 ($p = 0.0004$).

Table 15: Effectiveness of Imidacloprid + Moxidectin against *O. cynotis*

Treatment	Day 30		Day 60	
	Mite Count*	**Percent Effectiveness**	**Mite Count**	**Percent Effectiveness**
Group 1: imidacloprid + moxidectin	1.0	99.5%	NA	NA
Group 2: Control	230.2	NA	NA	NA
Group 3: imidacloprid + moxidectin	NA	NA	0.4	99.6%
Group 4: Control	NA	NA	86.6	NA

*Mite counts are geometric means.

Adverse Reactions: No adverse reactions were reported.

Conclusion: A single topical treatment of imidacloprid + moxidectin at the minimum label dose on cats provided 99.5% reduction of the ear mites (*O. cynotis*). A second treatment at 4 weeks resulted in 99.6% reduction in *O. cynotis*.

2) Clinical Evaluation of the Efficacy and Safety of Topically Applied ADVANTAGE Multi For Cats (Imidacloprid 10% + Moxidectin 1%) Against Ear Mites *(Otodectes cynotis*) Infesting Cats (Study #151.567, Report #75780)

Purpose: The objective of this study was to assess the efficacy and safety of imidacloprid + moxidectin applied topically to cats with ear mite infestations when administered by owners under actual use conditions.

Investigators and Locations:

Laird Laurence, DVM, Fredericksburg, TX
Roger Sifferman, DVM, Springfield, MO
Victor Manoharan, DVM, West Palm Beach, FL
Donnie Gamble, DVM, Summerville, SC
Robert Santos, DVM, Turlock, CA
Kenneth Brooks, DVM, Lodi, WI

Animals: A total of 332 cats from 93 households were evaluated for safety and 77 cats (53 imidacloprid + moxidectin and 24 active controls) were evaluated for effectiveness.

Table 16: Demographics

	Imidacloprid + Moxidectin	**Active Control**
Total #. of cats / # households	239/63	93/30
Single/Multi-cat households	16/47	10/20
# of cats by gender	113 male/126 female	42 male/51 female
Weight Ranges	1.2 – 17.6 pounds	2.6 – 16.4 pounds
Age Ranges	2 mo. – 18 yr.	3 mo. – 14 yr.

Treatment Groups:
(Doses based on labeled doses and weight ranges)
Treatment: ADVANTAGE MULTI for Cats
4.5 mg/lb (10 mg/kg) imidacloprid + 0.45 mg/lb (1 mg/kg) moxidectin
Active Control: REVOLUTION (selamectin)
2.7 mg/lb (6 mg/kg) selamectin

Route of Administration: Topical, applied to the skin on the back of the neck at the base of the skull

Frequency of Treatment: Twice with a 28-30 day treatment interval

Duration of Study: Approximately 56-60 days per case

Study Design: Veterinarians were masked to treatment group assignments. Veterinarians performed physical examinations on all cats at both study initiation and study conclusion. Cats with at least 5 ear mites observed by pre-treatment otoscopic examination were eligible for the study. Treatments were made by the pet owner on Day 0 and again on Day 28-30. In multi-cat households, all cats were treated with the same product. Post-treatment otoscopic exams were performed by the investigators for the observation of ear mites on Day 28-30 and on Day 56-60. Treatment success was based on the presence or absence of viable ear mites. Following treatment, owners observed their pets for untoward reactions for approximately 24 hours post-treatment.

Results: Imidacloprid + moxidectin provided ear mite effectiveness in 49 of 53 cats (92.5%) following one treatment and in 52 of 53 cats (98.1%) after the second treatment. The active control product provided ear mite effectiveness in 22 of 24 cats (91.7%) following one treatment and in 23 of 24 cats (95.8%) after the second treatment.

Adverse Reactions: Table 17 shows the post-treatment adverse reactions reported by owners and the number of cats per group with at least one occurrence of the indicated sign.

Table 17: Adverse Reactions

Clinical Observation	**Imidacloprid + Moxidectin N = 239**	**Active Control N = 93**
Lethargy	4 (1.7%)	0
Disoriented	1 (0.4%)	0
Hypersalivation	1 (0.4%)	0
Diarrhea	0	1 (1.1%)

Conclusions: The field study confirmed the effectiveness and safety of imidacloprid + moxidectin when administered to cats with ear mite (*O. cynotis*) infestations. One treatment or two treatments approximately 30 days apart both provided greater than 90% effectiveness against *O. cynotis.*

3. TARGET ANIMAL SAFETY:

1) Dermal Dose Tolerance Study with the Imidacloprid/Moxidectin Topical Solution in the Cat (Study #150.880, Report #75169) Good Laboratory Practice (GLP) study

Purpose: The objective of this study was to demonstrate the safety of imidacloprid + moxidectin topical solution when administered topically to cats at ten times (10X) the recommended dermal unit dosage.

Study Director: R. D. Jones, DVM, PhD

Location: Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS

Animals: 16 cats (4 females and 4 males per treatment group), approximately 4 to 5 months old and 1.8 to 3.9 kg (4.0 – 8.6 lbs)

Dosage: 10X the recommended dermal unit dosage or a comparable volume of mineral oil as a control. The recommended dermal unit dosage provides a minimum of 10 mg/kg imidacloprid + 1.0 mg/kg moxidectin.

Route of Administration: Topically, on the skin on the back of the head and neck, between the shoulder blades

Frequency of Treatment: One application

Duration of Study: 18 days

Variables Measured: Clinical observations were made at 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours post-treatment. Beginning on Day 1 clinical observations were then made twice daily. The cats were weighed pre-study and on Day 17. Blood was drawn from each cat pre-study and on Days 1 and 17 for hematology and clinical chemistry profiles.

Results: Following application of the test article, two cats did limited grooming of the application area and salivated slightly. One treated cat had a decreased appetite on the day of treatment.

Treated cats had mild elevations of mean alanine aminotransferase and alkaline phosphatase compared to the control. Mean red blood cell counts and hematocrits were lower in the males of the treated group. Group means of these variables were within normal limits.

Conclusions: A single topical administration of imidacloprid + moxidectin topical solution at 10X the recommended dose was associated with mild, transient salivation in 2 of 8 healthy juvenile cats. Salivation immediately followed grooming.

2) The Safety of Imidacloprid/Moxidectin Spot-On in 9 week-old Kittens.
(Study # 151.691, Report #201322) GLP laboratory study

Purpose: The objective of this study was to demonstrate the safety of 10.0% imidacloprid + 1.0% moxidectin administered topically to kittens at once a month intervals for three months.

Study Director: S. M. Ensley, DVM, PhD

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 48 Domestic Shorthair kittens (24 females/24 males), 61 to 64 days of age weighing 0.7 – 1.2 kg (1.5 – 2.6 lbs) at initial treatment

Dosages: Kittens were treated topically with 1X, 3X and 5X multiples of the maximum 1X dose of imidacloprid + moxidectin. Mineral oil served as a control.

Table 18: Dosage/Treatment Groups

Treatment Group	**Dose of Imidacloprid + Moxidectin**	**Number and Sex of Animals**
1	1X (0.33 mL/kg)	12 (6M/6F)
2	3X(0.99 mL/kg)	12 (6M/6F)
3	5X (1.65 mL/kg)	12 (6M/6F)
4	Control (mineral oil)	12 (6M/6F)

1X dose for this study = label dose volume (0.23mL) ÷ body weight (kg) of smallest

kitten in the 1X treatment group (0.7 kg).

Route of Administration: Topical, applied to 1 - 4 different sites on the dorsal mid-thoracic region. To minimize oral ingestion, each kitten wore an appropriately sized, non-restraining, liquid-resistant, spandex jacket with an attached dermal shield for four hours post-treatment.

Frequency of Treatment: Once every 28 days for three consecutive treatments (Days 0, 28 and 56)

Duration of Study: 58 days

Variables Measured: Clinical observations were conducted twice daily, except for days 0, 28, and 56, when observations were conducted at pre-dosing, immediately post-dosing (within 1-15 minutes), 1, 2, 4, and 6 hours post-dosing. Physical exams were performed on Days -7, 1, 29, and 58. Kittens were weighed on Days -7, -1, 0, 7, 14, 21, 28, 35, 42, 49, and 56. Food consumption was recorded daily for each kitten beginning on Day -4 through Day 58. Blood was drawn from each kitten on Days -4, 1, 29, and 58 for hematology and clinical chemistry profiles. Necropsies were conducted on Days 58, 59, 62, and 63, and gross pathologic examination performed, as well as histopathology.

Statistical Analysis: Body weight, food consumption, clinical pathology, and continuous urinalysis variables were each modeled using a repeated measures analysis of covariance. Each model included terms for treatment, time, sex, treatment-by-time, treatment-by-sex, and treatment-by-time-by-sex. The pre-treatment value for the response variable was used as a covariate in each of the models. Categorical urinalysis variables were analyzed using generalized estimating equations (GEE). In these GEE models, the only covariate included was treatment. Organ weight was modeled using an analysis of variance. Each model included terms for treatment, sex, and treatment-by-sex.

Results: *Clinical Observations*: Lethargy was observed in 1 kitten from the 3X group and 1 from the 5X group on the day after initial treatment; the kitten from the 3X group was also disoriented and ataxic following a difficult blood sample collection, while the kitten from the 5X group had rapid breathing. One kitten from the 5X group had a slow pupillary light response the day after treatment, and one had tremors the day after treatment. Hypersalivation was seen in one kitten from the 5X group approximately six hours post-treatment. One kitten from the 3X group was scratching at the treatment site 2 days after treatment. Slight cough was noted in 7 different kittens (2-0X, 2-1X, and 3-5X) during the 13-day period following the first treatment. All treated kittens had matted hair up to 2 days after each treatment.

Histopathology: There was granulomatous inflammation at the application sites in 3 kittens from the 1X group. Kittens in all groups were vaccinated in the intrascapular

area on Day 8 of the study. Due to the vaccine's proximity to the application site, a definitive cause of the granulomatous reaction could not be determined. Pulmonary inflammation (1-5X kitten) and lymphoid hyperplasia (2-1X kittens and 4-3X kittens) were seen in treated kittens; the relationship to product application is undetermined.

Conclusions: Imidacloprid + moxidectin was well tolerated following topical administration to nine-week-old kittens when given at the maximum recommended label dose every 28 days for three consecutive treatments. Clinical observations were seen primarily in the 3X and 5X dose groups and included lethargy, ataxia, disorientation, tremors, rapid breathing, decreased pupillary light response, hypersalivation and scratching at the application site.

3) Safety Evaluation of Imidacloprid/Moxidectin Spot-On in Cats with Experimentally-Induced *Dirofilaria immitis* Infections (Study #151.089, Report #201306) GLP laboratory study

Purpose: The objective of this study was to demonstrate the safety of 10.0% imidacloprid + 1.0% moxidectin following topical administration to cats with adult heartworm infections.

Study Director: S. M. Ensley, DVM, PhD

Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 27 heartworm-infected Domestic Shorthair Cats (14 females/13 males), approximately 13 months-old and 2.8 to 6.0 kg (6.2 to 13.2 lbs) at initial treatment

Heartworm Infection: Young adult cats were subcutaneously infected with third-stage *D. immitis* larvae and then maintained for ample time for maturation of surviving larvae into adult heartworms. At 243-245 days post-infection, immunoserology (antibody and antigen) and echocardiography were performed to identify cats with adult heartworm burdens similar to naturally-acquired infections.

Dosage: One group of heartworm-infected cats was treated topically with ADVANTAGE MULTI for Cats at the label dose, once every 28 days, for three consecutive treatments. A second group was treated topically, once, at 5X the label dose. A third group served as the control and was treated topically with mineral oil as a placebo once every 28 days for three consecutive treatments.

Table 19: Dosage/Treatment groups

Treatment Group	**Dose of Imidacloprid + Moxidectin**	**Number and Sex of Animals**
Mineral oil	0X (1X volume)	9 (4M/5F)
Imidacloprid/Moxidectin	1X	9 (4M/5F)
Imidacloprid/Moxidectin	5X	9 (5M/4F)

1X for this study was the labeled dose rate

Route of Administration: Topical, applied to the skin on the back of the head, neck, and between the shoulder blades.

Frequency of Treatment: 0X and 1X cats were treated once every 28 days for three treatments. The 5X group was treated once.

Duration of Study: 12 months (including infection, maturation, and acclimation); Treatment phase lasted 84 days.

Variables Measured: Physical examinations were performed on Days -21, 1, 29, 57, and 74. Blood was drawn for hematology and coagulation on study Days -19, 22, 38 (5X group only) and 84. Clinical observations were made twice daily except on treatment days when cats were observed before and approximately 1, 2, 4, and 6 hours after dosing. Necropsy and heartworm recovery were performed on Day 38 for the 5X group and Day 84 for the 0X and 1X groups.

Statistical Analysis: Body weight and hematology variables were each modeled using a repeated measures analysis of covariance. Each model included terms for treatment, time, sex, treatment-by-time, treatment-by-sex, and treatment-by-time-by-sex. The pre-treatment value for the response was used as a covariate in each of the models. The adult heartworm counts for the 0X and 1X groups were modeled using an analysis of variance. Each model included terms for treatment, sex, and treatment-by-sex.

Results: *Clinical Observations*: Sporadic vomiting and labored breathing were observed in cats from each group, including control. Although labored breathing was seen more frequently in the 1X dose group, no cats required treatment.

Gross Pathology and Heartworm Recovery at Necropsy: Multiple zones of pulmonary discoloration were the only gross lesions observed at necropsy. Adult heartworms were recovered from 23 of 27 cats. Infections in individual cats ranged from zero to ten adult heartworms. Treatment group geometric means ranged between 2.74 and 3.24 adult heartworms (See Table 20). Each recovered heartworm was alive and motile. There was no statistical difference between treatment groups in the number of adult heartworms recovered at necropsy ($p = 0.66$).

Table 20: Adult heartworms recovered at necropsy

Treatment group	**# of cats per group**	**# of cats with worms**	**Worm range (Min, Max) for non-zero counts**	**Geometric Mean number of worms**
0X	9	7	(1, 10)	2.74
1X	9	9	(1, 7)	2.86
5X	9	7	(4, 10)	3.24

Conclusions: The topical application of imidacloprid + moxidectin to experimentally heartworm-infected cats, either at the recommended label dose for three consecutive

monthly treatments or at 5X the recommended label dose for one treatment, was well tolerated.

4) Clinical Safety Evaluation of Imidacloprid + Moxidectin Applied Dermally to Cats (Study #151.251, Report #75279)

Purpose: The objective of this study was to assess the safety of topically-applied imidacloprid + moxidectin in cats when administered by the cat owners under the conditions of actual field-use.

Investigators and Locations:
Richard Mauldin, DVM, Oklahoma City, OK
Lisa Arthur, DVM, Charlotte, NC
Craig Staehle, DVM, O'Fallon, MO
Roger Becker, DVM, Independence, MO

Animals: A total of 151 cats from 60 different households completed the study

Table 21: Demographics

	Imidacloprid + Moxidectin	**Active Control**
Total No. of cats & households	113 cats 42 households/clients	38 cats 19 households/clients
Weight Ranges	2.2 to 20 lbs	2.1 to 14.8 lbs
Age Ranges	3 mo to 18 years	2.5 mo to 13 yr

Treatment Groups:
(Doses based on labeled doses and weight ranges)
Treatment: ADVANTAGE MULTI for Cats
4.5 mg/lb (10 mg/kg) imidacloprid + 0.45 mg/lb (1 mg/kg) moxidectin
Active Control: REVOLUTION (selamectin)
2.7 mg/lb (6 mg/kg) selamectin

Route of Administration: Topical

Frequency of Treatment: Once monthly for 3 consecutive months

Duration of Study: Approximately 62-68 days per case

Study Design: Four populations of client-owned cats served as test subjects: single cat household/ domestic, single cat household/ purebred, multiple cat household/

domestics, multiple cat household/ with at least 1 purebred. Both clients and veterinarians were masked to treatment group assignments. All treatments were administered by pet owners.

Attending veterinarians performed physical examinations on all cats at both study initiation and study conclusion. 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 28 days of the final treatment, cats were returned to the clinic for a post-study physical examination and assessment.

Results: *Physical Examinations*: A comparison of pre- and post-study physical examination results revealed no treatment-induced abnormalities in study participants.

Post-Treatment Observations: Table 22 shows post-treatment signs reported by owners and the number of cats per group with at least one occurrence of the indicated sign.

Table 22: Adverse Reactions

Clinical Observations	**Imidacloprid/ Moxidectin N=113**	**Active Control N=38**
Lethargy (protracted sleeping, poorly responsive)*	3 (2.7%)	0
Hypersalivation, excessive to mild (within the first hour after treatment)	3 (2.7%)	0
Discomfort (scratching at the treatment site, rubbing, head-shaking, vocalizing (within 6 hours of treatment)	5 (4.4%)	0
Behavioral changes (agitated, excessive grooming, hiding, pacing, spinning)	9 (8.0 %)	1 (2.6%)
Coughing and gagging	1 (0.9%)	0
Polydipsia	3 (2.7%)	0
Dry, white residue at the application site	0	2 (5.5%)
Damp, wet, oily, or greasy appearance to the application site	16 (14.2%)	0

* The three lethargic cats were from the same household and included one 13-yr-old cat in good health, one 15-yr-old, FIV positive cat in good health, and one 15-yr-old, underweight cat in fair health. Lethargy was noted for 24-36 hours after the first treatment; one cat was unsteady at 48 hours. These cats were not on other medications.

Conclusions: Topical administration of imidacloprid + moxidectin was generally well

tolerated, but resulted in the following adverse reactions: behavioral changes, discomfort, salivation, polydipsia, and lethargy in geriatric cats. Signs were self-limiting and did not require medical intervention. The occurrence of significant lethargy in one underweight, 15-year-old cat and in a healthy, 15-year-old, FIV positive cat justifies the label warning: Do not use in sick, debilitated, or underweight cats and the label precaution: Use of this product in geriatric patients with subclinical conditions has not been adequately studied. Several otherwise healthy, thin, geriatric cats experienced prolonged lethargy and sleepiness after using this drug."

5) Evaluation of the Safety of Imidacloprid / Moxidectin Topical Solution in Kittens (Report #75167) GLP laboratory study

Purpose: The objective of this study was to evaluate the safety of imidacloprid + moxidectin (10.0% imidacloprid/1.0% moxidectin) following topical application to kittens.

Study Director: Albert Abraham, BVSc, PhD

Study Location: Intervet, Inc. (Formerly owned and operated by Bayer, Inc.), DeSoto Animal Research Farm, DeSoto, KS

Animals: 48 domestic shorthair kittens (24 males/24 females), 9 weeks old and 737 to 1070 grams on Study Day -1, 12 kittens (6 per sex) per group

Dosages: Doses tested were 0X, 1.7X, 5.2X and 8.7X the maximum label dose (0.26 mL/kg). The control group received mineral oil at the 5X volume.

Route of Administration: Topical

Frequency of Treatment: Once every two weeks for six consecutive treatments on Days 0, 14, 28, 42, 56 and 70
.
Duration of Study: 85 days

Variables Measured: Clinical observations were made twice daily except on treatment days (Days 0, 14, 28, 42, 56 and 70) when cats were observed pre-dosing and at approximately 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dosing. Kittens were weighed pre-dose and on Days 13, 27, 55, 69, 77, and 83. Food consumption was recorded daily for each kitten on Days -14 through 84. Blood was drawn from each kitten pre-dose and on Days 3, 15, 29, 43, 57, 71, and 83 for hematology and clinical chemistry profiles. Each kitten received a physical exam pre-dose and on Day 83. Necropsies were conducted on Days 84 and 85 and gross pathologic examination performed. Bone marrow smears were made and tissues from the 8.7X and control group animals were processed for histopathology.

Results:
Clinical Observations: An 11-week-old, 1.2 kg healthy kitten in the 8.7X group apparently ingested an unknown amount of the drug at the second treatment and developed the following clinical signs: mydriasis, salivation, depression, vomiting, unsteadiness, rapid to slow to difficult breathing, poor pupillary response, generalized tremors, inability to move, and nystagmus. The kitten was euthanized two days post-dosing. Necropsy findings were limited to marked acute tracheal inflammation, mild liver vacuolization, and mild thymic necrosis.

One kitten in the 5.2X group was lethargic, salivating, squinting, and had ocular discharge at 1 and 2 hours after the first treatment. The squinting lasted 12 hours. Another 5.2X kitten had excessive salivation immediately, and at hours 1, 2 and 4 after the third treatment. She had transient mydriasis at the 4-hour check and a poor appetite that day.

A kitten in the 1.7X group had mydriasis for up to a day following the second and third treatments.

One kitten in the control group had slow respiration and unsteady locomotion in the afternoon the day after the second treatment. It had vomited, had diarrhea, and a poor appetite that day. Another control kitten was depressed at hour 2 after the third treatment.

Body Weights and Food Consumption: No differences were noted between groups.

Hematology, Chemistry, Necropsy: After 6 weeks of treatment, treated kittens (especially the 5.2X group) had slightly lower red blood cell counts and higher mean corpuscular volume (MCV) values than the controls. The 5.2X kittens also had slightly higher mean alanine aminotransferase values. No differences were noted between groups on necropsy or histopathology.

Conclusions: Imidacloprid + moxidectin was well tolerated following topical administration to nine-week-old kittens at 1.7X the maximum labeled dose. Clinical observations were seen primarily in the 5.2X and 8.7X dose groups and included lethargy, hypersalivation, and mydriasis. If ingested, imidacloprid + moxidectin can cause significant toxicity, including death. Additional studies were conducted to evaluate the safety of the product in case of accidental ingestion (see Studies 6 and 7 below).

6) Oral Dose Study with Imidacloprid/Moxidectin Spot-On in 8-Week-Old Kittens (Study #151.735, Report #75778) Pilot study, non-GLP laboratory study

Purpose: The objective of this study was to provide information regarding the oral safety of imidacloprid + moxidectin topical formulation in 8-week-old kittens.

Study Director: S. M. Ensley, DVM, PhD

Location: Bayer CropScience LP, Stilwell, KS

Animals: 14 Domestic Shorthair kittens (7 females and 7 males), 8 weeks of age and 0.5 – 1.1 kg (at treatment)

Dosage: Thirteen kittens were dosed orally, once, with the maximum topical dose of imidacloprid + moxidectin. One female kitten was maintained as an untreated, age-matched control.

Table 23: Dosage/Treatment groups

Treatment Group	Treatment	Number of Kittens
1	10% Imidacloprid + 1.0% Moxidectin at 0.46 mL/kg*	13
2	Control (non-treated)	1

*1X dose for this study = label dose volume (0.23 mL) ÷ body weight (kg) of smallest kitten in treatment group (0.5 kg)

Route of Administration: Oral via a syringe

Frequency of Treatment: Single treatment

Duration of Study: 18 days

Variables Measured: Clinical observations, body weight, food consumption, gross and histopathology

Results: On the day of treatment, post-dosing clinical signs included: vomiting (10 of 13 kittens), labored breathing (5 of 13 kittens), slight whole-body tremors (2 of 13 kittens) and decreased activity (1 of 13 kittens). Salivation was observed at dosing (9 of 13 kittens) and later in the day (2 of 13 kittens). On post-treatment Day 6, a treated kitten was found dead; this kitten displayed vomiting, labored breathing, and whole body tremors immediately post-dosing. The only clinical observation at the time of death was salivation.

Relative to pre-treatment intake, treated kittens experienced decreased food consumption on study Days 1 through 7. Eight treated kittens also lost body weight (3-18%) during the interval between Days -1 and 7.

Necropsies were performed on six kittens, including the one found dead. No gross lesions were noted in any animal. Histopathology showed minimal to marked changes in the liver in all kittens. Centrilobular congestion and intracytoplasmic vacuoles were observed in the kitten found dead. Periportal intracytoplasmic vacuolation was noted

in the remaining kittens, including the control. The severity was greater in the treated kittens.

Conclusions: The oral administration of imidacloprid + moxidectin to 8-week-old kittens induced clinical signs including salivation, vomiting, labored breathing, tremors, decreased activity, and inappetence. One treated kitten was found dead on the sixth day post-treatment; the cause of death could not be conclusively determined. This study supports the age and weight restrictions on the label.

7) Oral Safety with Imidacloprid/Moxidectin Spot-On in Nine-Week-Old Kittens (Study #150.690, Report #201119) GLP laboratory study

Purpose: The objective of this study was to evaluate the safety of 10.0% imidacloprid + 1.0% moxidectin in kittens following oral administration of the maximum 1X topical dose.

Investigator: S. M. Ensley, DVM, PhD

Study Location: Bayer CropScience LP, Toxicology, Stilwell, KS

Animals: 24 Domestic Shorthair kittens (12 females/12 males), 60 to 64 days of age, and between 0.9 – 1.4 kg (1.9 - 3.1 lbs)

Dosage: Kittens were dosed orally, once, with the maximum 1X topical dose of imidacloprid + moxidectin. The control group received tap water.

Table 24: Dosage/Treatment groups

Treatment Group	**Dose of Imidacloprid + Moxidectin**	**Number and Sex of Kittens**
1	1X (0.26 mL/kg)*	12 (6M/6F)
2	Control (water)	12 (6M/6F)

*1X dose for this study = label dose volume (0.23mL) ÷ body weight (kg) of smallest kitten in the treatment group (0.9 kg)

Route of Administration: Oral

Frequency of Treatment: Single treatment

Duration of Study: 14 days

Variables Measured: Body weights and physical examinations were performed during acclimation and on Days 1 and 14. Kittens were observed for clinical signs twice daily except on Day 0 when they were observed 1, 2, 4, and 6 hours after treatment.

Statistical analysis: Body weight and food consumption were each modeled using a

repeated measures analysis of covariance. Each model included terms for treatment, time, sex, treatment-by-time, treatment-by-sex, and treatment-by-time-by-sex. The pre-treatment value for the response variable was used as a covariate in each of the models.

Results: Hypersalivation (8 of 12 kittens), vomiting (12 of 12 kittens), and tremors (1 of 12 kittens) were observed immediately post-treatment in the treated kittens. On post-treatment Days 1 through 12, anorexia (decrease in daily food consumption to less than 30% of the pre-treatment daily average) and partial inappetence (decrease in daily food consumption to between 30 – 80% of the pre-treatment daily average) were present in 10 of 12 kittens and 2 of 12 kittens, respectively. The mean food consumption in the treated group was significantly less than in the placebo group for the first week post-treatment ($p < 0.001$). No significant difference between the two groups was found in the second week post-treatment ($p = 0.8$). The mean body weight in the treated group was significantly less than that in the placebo group at Day 7 ($p < 0.001$) and at Day 14 ($p = 0.011$).

Conclusions: Accidental oral administration of imidacloprid + moxidectin causes self-limiting, post-treatment clinical signs (hypersalivation, vomiting, tremors, appetite suppression, and weight loss). The product should not be ingested. The product label restricts use to cats 9 weeks or older and 2 lbs body weight or greater.

4. HUMAN FOOD SAFETY:

This drug is intended for use in cats, 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.

5. USER SAFETY:

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

"Not for human use. Keep out of the reach of children.
Children should not come in contact with the application site for 30 minutes after application.
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 eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or 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, moxidectin, or imidacloprid 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."

The bolded human warnings: "**Children should not come in contact with the application site for 30 minutes after application**" and "**Wash hands thoroughly with soap and warm water after handling**" were based on Human Risk Assessment determinations. The risk assessment estimated the potential human (adult and toddler) acute and chronic dermal, and toddler hand-to-mouth oral exposure levels, and levels of concern from contact with a treated cat. The risk assessment factors (pet surface-to-human transfer dose, dermal absorption, and No Observable Adverse Effect Levels) were derived from data for imidacloprid, moxidectin, or related compounds in toxicity or pharmacokinetic studies in laboratory animals, a pharmacokinetic study in human volunteers, or cotton glove stroking (drug recovery) studies in cats.

6. 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 Cats, when used according to the label, is safe and effective for the following indications: ADVANTAGE MULTI for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. ADVANTAGE MULTI for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations. ADVANTAGE MULTI for Cats is also indicated for the treatment and control of ear mite (*Otodectes cynotis*) infestations and the following intestinal parasites:

Intestinal Parasite		**Intestinal Stage**		
		Adult	**Immature Adult**	**Fourth Stage Larvae**
Hookworm Species	*Ancylostoma tubaeforme*	X	X	X
Roundworm Species	*Toxocara cati*	X		X

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 monitor the safe use of the product.

b. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. Exclusivity is based on the conduct of new studies for substantial evidence of effectiveness and new target animal safety data.

c. Patent Information:

ADVANTAGE MULTI for Cats is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
US 6,232,328	May 12, 2015
US 6,001,858	Nov. 27, 2015

7. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

Package Insert
Calendar Reminder Stickers
Tube Labels
Foil Backing for Blister Pack
Foil Pouch (for 0.23 mL size only)
Dispensing Container Carton (Multi Carton)
Display Carton
Shipping Labels