Date of Approval: October 31, 2013

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-254

ADVANTAGE MULTI for Cats

Imidacloprid + moxidectin

Solution

Ferrets

This supplement provides for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. ADVANTAGE MULTI for Cats kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations on ferrets.

Sponsored by:

Bayer HealthCare LLC
Animal Health Division

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I. 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. Proprietary Name

ADVANTAGE MULTI for Cats

D. Established Name

Imidacloprid + moxidectin

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Solution

G. Amount of Active Ingredient

10% imidacloprid + 1% moxidectin

H. How Supplied

Applicator tube size and applications per package
3 x 0.23 mL tubes (cats only)
6 x 0.4 mL tubes (cats and ferrets)
6 x 0.8 mL tubes (cats only)

I. Dispensing Status

Rx

J. Dosage Regimen

The recommended minimum dose for a ferret is 9 mg/lb (20 mg/kg) imidacloprid and 0.9 mg/lb (2 mg/kg) moxidectin, once a month, by topical administration.

Ferret (lb)	ADVANTAGE MULTI for Cats	Volume (mL)	Imidacloprid (mg)	Moxidectin (mg)
2.0 to 4.4	ADVANTAGE MULTI 9	0.4	40	4

Only the 0.4 mL applicator tube volume (ADVANTAGE MULTI 9) should be used in ferrets.

K. Route of Administration

Topical

L. Species/Class

Ferret

M. Indication

ADVANTAGE MULTI for Cats is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis.* ADVANTAGE MULTI for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations on ferrets.

N. Effect of Supplement

This supplement provides for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. ADVANTAGE MULTI for Cats kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations on ferrets.

II. EFFECTIVENESS

A. Dosage Characterization

The 0.4 mL dose of Advantage Multi for Cats (10% imidacloprid + 1% moxidectin) was selected for administration to ferrets for treatment of adult flea infestations caused by *Ctenocephalides felis* based on pilot laboratory studies. This volume delivers a total dose of 40 mg imidacloprid and 4 mg moxidectin.

1. Imidacloprid

A flea effectiveness study was conducted in ferrets using an imidacloprid dosage of 10 mg/kg body weight. Ferrets ranged in body weight between 0.8 and 1.6 kg. At this dose, effectiveness against adult flea infestations was greater than 90% only through Day 8 post-treatment.

Additional studies conducted in ferrets weighing between 0.6 kg and 2.0 kg demonstrated that a total imidacloprid dose of 40 mg per ferret (20.0 to 66.7 mg/kg) was safe and greater than 90% effective for the treatment of adult flea infestations for up to 30 days.

2. Moxidectin

The 0.4 mL size of ADVANTAGE MULTI for Cats (10% imidacloprid + 1% moxidectin) delivers a total of 4 mg moxidectin which provides between 2.0 and 6.7 mg/kg moxidectin in ferrets weighing between 0.6 and 2.0 kg. A minimum moxidectin dose of 2.0 mg/kg was found to be safe and 100% effective for the prevention of heartworm disease in ferrets when administered monthly.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study for the Prevention of Heartworm Disease (*Dirofilaria immitis*):

a. Title:

"Study to determine the Efficacy of Imidacloprid 10% / Moxidectin 1% Spot-on for Heartworm Prophylaxis in Ferrets" (Study Number: 144.714)

b. Investigator:

Dr. J. W. McCall
Athens, GA

c. Study Design:

(1) Objective:

The objective of this laboratory study was to evaluate the effectiveness of 10% imidacloprid + 1% moxidectin topical solution for the prevention of heartworm disease in ferrets experimentally infected with *Dirofilaria immitis*.

(2) Study Animals:

Twelve male ferrets, 7.5 months of age, weighing 1.2 - 2.1 kg. Each ferret was artificially infected with 25 infective, third-stage *D. immitis* larvae on Study Day -30. Ferrets were ranked by Study Day -1 body weight and randomly assigned to two treatment groups.

(3) Treatment Groups:

Group 1: 0.4 mL 10% imidacloprid + 1% moxidectin topical solution administered on Study Day 0
Group 2: Untreated control

(4) Dose and Route of Administration:

Topical application on the neck at the base of the skull on Study Day 0. Based on body weight, the moxidectin dose range was 1.9 - 3.3 mg/kg.

(5) Measurements and Observations:

Physical examinations were performed on Study Days -35 and -3. Ferrets were carefully observed post-treatment for any adverse events. Daily general health observations were recorded throughout the study. Ferrets were weighed on Study Days -1, 0, 90, and 124. Blood samples were collected for examination for *D. immitis* microfilariae and adult *D. immitis* antigen on Study Days -36 and 90. Each ferret was necropsied on Study Day 124 for recovery and counting of adult *D. immitis*.

(6) Statistical Methods:

Percent effectiveness was calculated by comparing the geometric mean number of heartworms recovered from the treated ferrets to those recovered from the control ferrets on Study Day 124.

d. Results:

The geometric mean worm count of the ferrets in Group 2 (untreated controls) was 17.2, indicating an adequate infection. No adult *D. immitis* were recovered at necropsy from any of the Group 1 ferrets receiving 10% imidacloprid + 1% moxidectin topical solution, resulting in 100% effectiveness. No microfilariae were observed and all blood samples were negative for *D. immitis* antigen from all ferrets on Study Days -36 and 90, indicating the ferrets had no exposure to *D. immitis* prior to the experimental infections.

e. Adverse Reactions:

No adverse reactions were reported in this study.

f. Conclusion:

A single treatment of 0.4 mL of 10% imidacloprid + 1% moxidectin topical solution is 100% effective for the prevention of heartworm disease in ferrets experimentally infected with *D. immitis*.

2. Laboratory Dose Confirmation Study for the Treatment of Flea Infestations Caused by *Ctenocephalides felis*:

a. Title:

"Efficacy of Advocate[1] Spot-On Imidacloprid 10% / Moxidectin 1% against Fleas (*Ctenocephalides felis*) on Ferrets (*Mustela putorius furo*)" (Study Number: 145.129)

[1] ADVOCATE is the tradename for ADVANTAGE MULTI for Cats marketed in the European Union.

b. Investigator:

Prof. Dr. A. Daugschies
Leipzig, Germany

c. Study Design:

(1) Objective:

To evaluate the effectiveness of 10% imidacloprid + 1.0% moxidectin topical solution administered as a one-time dose for the treatment of flea infestations on adult ferrets. Local tolerance and general safety was also assessed.

(2) Study Animals:

Sixteen ferrets (8 males and 8 females), 10 to 24 months of age, weighing between 0.8 and 2.0 kg. Each ferret was experimentally infested with 50 unfed adult fleas (*C. felis*) on Study Days -7, -1, 7, 14, 21, and 28. The ferrets were ranked from highest to lowest body weight on Study Day -7 and randomized to one of two treatment groups based on Study Day -6 flea counts.

(3) Treatment Groups:

Group 1: 0.4 mL 10% imidacloprid + 1% moxidectin topical solution administered on Study Day 0
Group 2: Untreated control

(4) Dose and Route of Administration:

Topical application on the neck at the base of the skull on Study Day 0. Based on body weight, the imidacloprid dose range was 20 – 50 mg/kg.

(5) Measurements and Observations:

Each ferret was infested with 50 unfed adult fleas (*C. felis*) on Study Days -7, -1, 7, 14, 21, and 28. Ferrets were combed for fleas on Study Days -6, 1, 8, 15, 23, and 30. Live fleas were removed and counted. Clinical assessment of physical condition, behavior, skin, cardiovascular and respiratory function, and fecal quality were recorded on Study Days -7,-1, 1, and 28. Local topical reactions at the application site were assessed on Study Days 7, 14, and 21. General health observations were recorded daily throughout the study.

(6) Statistical Methods:

Percent effectiveness was calculated by comparing the geometric mean number of live fleas recovered from the treated ferrets to those recovered from the control ferrets on Study Days 8, 15, 23, and 30.

Because the calculation of the geometric mean involved taking the logarithm of the live flea count of each ferret, and some of the live flea

counts were equal to zero, a 1 was added to the flea count for every ferret in both groups. This constant (1) was subtracted from the resultant calculated geometric mean prior to calculating percent effectiveness. Wilcoxon-Mann-Whitney test was used to compare the treatment group with the untreated group using a two-sided test.

d. Results:

Table 1: Summary of results by study day

Study Day	Group 1 Geometric Mean Live Flea Counts	Group 2 Geometric Mean Live Flea Counts	Group 1 Percent Effectiveness	p-Values
1	0	23.6	100	0.0004
8	0	32.1	100	0.0004
15	0	29.7	100	0.0004
23	0.5	20.6	97.6	0.0008
30	2.7	29.4	90.8	0.0027

e. Adverse Reactions:

No adverse reactions were reported in this study.

f. Conclusion:

A single treatment of 0.4 mL 10% imidacloprid + 1.0% moxidectin topical solution was > 90% effective for treatment of flea infestations on ferrets for one month.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety:

1. Laboratory Margin of Safety Study:

a. Title:

"Safety Evaluation of Imidacloprid 10% + Moxidectin 1% Topical Solution on Young Adult Ferrets" (Study Number: 145.355)

b. Study Director:

Timothy J. Madsen, BA
Auxvasse, MO

c. Study Design:

(1) Objective:

The objective of this laboratory study was to evaluate the safety of 10% imidacloprid + 1% moxidectin topical solution in young adult ferrets following topical application at 14-day intervals for four consecutive treatments.

(2) Study Animals:

Eight ferrets (4 intact males and 4 spayed females), approximately 9 months of age, with body weights ranging from 0.9 kg to 1.8 kg at the start of the study.

(3) Treatment Groups:

Group 1: Five tubes (total of 2 mL) of 0.4 mL 10% imidacloprid + 1% moxidectin topical solution administered on Study Days 0, 14, 28 and 42.
Group 2: – Untreated control

Table 2: Minimum and maximum imidacloprid and moxidectin dosages administered

Treatment Group	Number Of Animals	Imidacloprid Dose (mg/kg)	Moxidectin Dose (mg/kg)
Control (untreated)	1 M/ 1F	0	0
5X volume (treated)	3 M/ 3F	112 to 235 mg/kg	11 to 23 mg/kg

(4) Dose and Route of Administration:

Topical application on the dorsal neck between the base of the skull and the cranial aspect of the shoulder blades applied once every 14 days for four consecutive treatments (Study Days 0, 14, 28, and 42). See Table 2 for the minimum and maximum doses administered.

(5) Measurements and Observations:

Measured variables included clinical observations, physical examination, body weight, food and water consumption, complete blood counts, chemistry profiles, gross necropsy, and histology. Group 2 was used as a control for the necropsy and histology portion of the study; the other variables were not measured in the control group.

(6) Statistical Methods:

The analysis of study results did not include inferential statistics due to the small number of animals in the study design.

d. Results:

Physical examination findings and food and water consumption were within acceptable limits throughout the study, with slight increases in body weight noted for all animals during the exposure period.

e. Adverse Reactions:

The following adverse reactions were observed during the study: Wet, matted, and/or greasy hair, shaking of the head and/or body, rubbing of dose site on cage, and shedding. Slight increases in phosphorous, potassium, aspartate aminotransferase (AST), and glucose were observed

during the study. No clinical signs were associated with any alterations in blood work.

f. Conclusion:

The 10% imidacloprid + 1% moxidectin topical solution, administered at 5 times the recommended dose volume every 14 days for four consecutive treatments, was safe in nine-month-old ferrets.

B. Oral Safety:

1. Laboratory Oral Safety Study:

a. Title:

"General Safety of Imidacloprid (10%) + Moxidectin (1%) Orally Administered to Pediatric Ferrets" (Study Number: 152.547)

b. Study Director:

Timothy J. Madsen, BA
Auxvasse, MO

c. Study Design:

(1) Objective:

The objective of this laboratory study was to assess the safety of 10% imidacloprid + 1% moxidectin topical solution administered orally to pediatric ferrets with body weights greater than 450 grams.

(2) Study Animals:

Sixteen ferrets (8 intact males and 8 intact females), 78 - 101 days old (11.1 - 14.4 weeks) and 0.5 - 0.8 kg body weight on the day of dosing.

(3) Treatment Groups:

Group 1:0.4 mL 10% imidacloprid + 1% moxidectin topical solution administered on Study Day 0
Group 2: Control (0.4 mL of tap water) on Study Day 0.

(4) Dose and Route of Administration:

Oral administration once on Study Day 0. Based on body weight, the imidacloprid and moxidectin dose ranges were 48.3 - 81.0 mg/kg (22.0 - 36.8 mg/lb and 4.8 - 8.0 mg/kg (2.2 - 3.7 mg/lb), respectively.

(5) Measurements and Observations:

Physical examinations were conducted on Study Days -7, 1 and 13. Body weight was obtained on Study Days -7, -1, 7 and 14. Clinical observations were conducted on Study Days 0 to 14.

(6) Statistical Methods:

Body weights were analyzed by a repeated measures analysis of covariance, with treatment, sex, day, treatment by sex, sex by day, treatment by day, and treatment by sex by day terms in the model as fixed effects. Pre-treatment values were used as a covariate and remained in the model regardless of significance.

d. Results:

Physical examination findings and body weight were within acceptable limits throughout the study. There were no clinically relevant or statistically significant differences in body weight between control and test article groups or in individual ferrets during the study.

e. Adverse Reactions:

Mild, self-limiting abnormal clinical signs were observed immediately following oral administration of 10% imidacloprid + 1% moxidectin topical solution in three of eight ferrets in the test article group and included emesis (one ferret) and ataxia (two ferrets). Emesis and ataxia all resolved without supportive care on the same day the test article was administered.

f. Conclusion:

Oral administration of 10% imidacloprid + 1% moxidectin topical solution at a dose of 0.4 mL to pediatric ferrets resulted in clinical signs of emesis and ataxia, which resolved without supportive care.

C. Field Safety:

1. Field Safety Study:

a. Title:

"Clinical Evaluation of the Field Safety of 10% Imidacloprid + 1% Moxidectin Topical Solution in Ferrets" (Study Number 152.437)

b. Investigators:

Deborah Cottrell, DVM Newberry, FL	Natalie Antinoff, DVM, DABVP Houston, TX
Jerry Murray, DVM Dallas, TX	Lauren Powers, DVM, DABVP Huntersville, NC

c. Study Design:

(1) Objective:

The purpose of this study was to evaluate the safety of 10% imidacloprid + 1% moxidectin topical in client-owned ferrets and to evaluate whether ferret owners could safely apply the product.

(2) Study Animals:

One hundred thirty-one (131) ferrets (62 neutered males and 69 spayed females), 3 months to 7 years of age, and weighing from 0.5 to 1.9 kg.

(3) Treatment Groups:

All ferrets were administered one tube (0.4 mL) of 10% imidacloprid + 1% moxidectin topical solution dispensed from market formulation pre-filled pipettes. A control group was not used in this study.

(4) Dose and Route of Administration:

A dose of 0.4 mL was administered topically by owners one time to each ferret on the dorsal neck between the base of the skull and the cranial aspect of the shoulder blades.

(5) Measurements and Observations:

Physical examinations were conducted pre-treatment and Study Day 14 by the Study Investigators. Owner observations were conducted at the time of treatment, at 30 minutes post-treatment, and daily for 14 days post-treatment.

(6) Statistical Methods:

Descriptive statistics by site as well as overall were performed.

d. Results:

Physical examination findings were within clinically acceptable limits throughout the study.

e. Adverse Reactions:

No serious adverse reactions were observed in the study. Adverse reactions in ferrets following treatment included: pruritus/ scratching, scabbing, redness, stiffening of the hair, and inflammation at the treatment site; lethargy; and chemical odor. These adverse reactions resolved without additional therapy.

Three human adverse reactions were reported. An owner's finger became red following skin contact with the product. One owner reported a headache caused by the chemical odor of the product. One owner reported a tingling sensation of the lips after kissing the treatment site.

f. Conclusions:

This field study demonstrated that 0.4 mL of 10% imidacloprid + 1% moxidectin topical solution is safe when applied topically to ferrets. The

study also demonstrated that owners can safely apply the product to their ferret.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in ferrets and 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.

V. 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. 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 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, 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 Cats, when used according to the label, is safe and effective for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis*. ADVANTAGE MULTI for Cats kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment of flea infestations on ferrets.

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:

This supplemental approval for ADVANTAGE MULTI for Cats qualifies for SEVEN years of exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the Federal Food, Drug, and Cosmetic Act (the act) because it is a designated new animal drug under section 573(a) of the act. Except as provided in section 573(c)(2) of the act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as ADVANTAGE MULTI for Cats in ferrets. Because the supplemental approval included safety and effectiveness studies, this drug also qualifies for three years of exclusivity under section 512(c)(2)(F)(iii) of the act. This exclusivity begins as of the date of our approval letter and only applies to the use of ADVANTAGE MULTI for Cats in ferrets. The exclusive marketing rights and applicable exclusivity run concurrently.

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.