Date of Approval: January 9, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-435

ADVANTUS

Imidacloprid

Chewable Tablet

Dogs

ADVANTUS kills adult fleas and is indicated for the treatment of flea infestations on dogs and puppies 10 weeks of age and older and weighing 4 pounds or greater.

Sponsored by:

Piedmont Animal Health

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I. GENERAL INFORMATION

A. File Number

NADA 141-435

B. Sponsor

Piedmont Animal Health
204 Muirs Chapel Road
suite 200
Greensboro, NC 27410

Drug Labeler Code: 058147

C. Proprietary Name

ADVANTUS

D. Established Name

Imidacloprid

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable tablet contains either 7.5 mg or 37.5 mg of imidacloprid

H. How Supplied

ADVANTUS is available in two strengths: 7.5 mg or 37.5 mg imidacloprid. Both strengths are packaged in 30 count bottles containing 30 flavored soft chews.

I. Dispensing Status

Over-the-counter (OTC)

J. Dosage Regimen

You should weigh your dog before giving this medication to make sure you are using the right size for your dog. Do not give to puppies younger than 10 weeks of age or to dogs weighing less than 4 pounds. Do not give more than one tablet a day.

Use the table to find the right dose for your dog:

Dosing Table

Body Weight	Dose	Soft Chew Strength
4-22 pounds	One soft chew	7.5 mg imidacloprid
23-110 pounds	One soft chew	37.5 mg imidacloprid

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

ADVANTUS kills adult fleas and is indicated for the treatment of flea infestations on dogs and puppies 10 weeks of age and older and weighing 4 pounds or greater.

II. EFFECTIVENESS

A. Dosage Characterization

The dose of imidacloprid is 0.34 mg/lb (0.75 mg/kg) administered orally. The dose is based on six exploratory, laboratory effectiveness studies to determine the lowest effective dose. The six exploratory effectiveness studies were conducted using the following doses: 30, 10, 6, 3, 1, 0.50, and 0.25 mg/kg body weight. Each study also contained a control group. Imidacloprid technical active in gel capsules was orally administered 24 hours after all dogs were infested with approximately 100 unfed adult fleas (*Ctenocephalides felis)*. Comb counts were conducted 24 hours after dosing. The number of live fleas removed during the comb counts was recorded.

All doses of imidacloprid were 100% effective against flea infestations at 24 hours post-dose (Table 1) based on comparing the arithmetic mean flea counts between treated and control dogs. Note that all studies used a live flea count at 24 hours post-dose. The knockdown effectiveness study also used a dead flea count at 4 and 6 hours post-dose.

Table 1. Calculated Percent Effectiveness from Adult Flea Counts.

Dose (mg/kg)	% Effectiveness: 4 hours	% Effectiveness: 6 hours	% Effectiveness: 24 hours
30	N/A	N/A	100*
10	N/A	N/A	100*
6	N/A	N/A	100*
3	N/A	N/A	100*
1	82.8°	100°	100*
0.5	56.7°	100°	100*
0.25	N/A	N/A	100*

°based on dead flea counts
*based on live flea counts

Because there were no drug-related adverse reactions noted during these studies at any dose level, a dose of 0.34 mg/lb (0.75 mg/kg) was selected as the safe and effective dose for additional evaluation. The rationale for this dose selection was based on the 100% effectiveness of the 0.5 and 1.0 mg/kg dose at 6 hours post dose and at least 50% effectiveness at 4 hours post dose. Although the 0.45 mg/lb (1.0 mg/kg) dose demonstrated promising activity at 4 hours post-dose, the lower 0.34 mg/lb (0.75 mg/kg) dose was selected to avoid unnecessary exposure while still maintaining effectiveness.

B. Substantial Evidence

1. Field Study

a. Title:

Field Study to Evaluate the Safety and Efficacy of Oral Imidacloprid for the Treatment of Cat Flea (*Ctenocephalides felis*) Infestations on Dogs. Study Number PAH-09-0040.

b. Investigators:

Locations and Investigators.

Dr. Gary Brotze New Braunfels, TX	Dr. Lynn Buzhardt Zachary, LA	Dr. William Campaigne Seguin, TX
Dr. Terry Clekis Bradenton, FL	Dr. Sam Geller Quakertown, PA	Dr. Edward Jezbera Riverside, CA
Dr. Andrew Krieger Manhattan Beach, CA	Dr. Kristi Lively Knoxville, TN	Dr. Amy Pilmer Fredericksburg, TX
Dr. Lynn Roberts Rural Hall, NC	Dr. Eddie Robinson Columbia, SC	Dr. David Scotton Greensboro, NC
Dr. Roger Sifferman Springfield, MO	Dr. Leonard Sigdestad San Bernardino, CA	Dr. Phillip Waguespack Baton Rouge, LA
Dr. Ginger Williams Eden, NC		

c. Study Design:

(1) Objective:

The objective of the study was to evaluate the field safety and effectiveness of daily oral imidacloprid chewable tablets for the treatment of cat flea (*C. felis*) infestations in dogs when administered for 14 consecutive days under actual use conditions.

(2) Study Animals:

There were 206 dogs (118 primary and 88 secondary) administered imidacloprid chewable tablets and 125 control dogs (82 primary and 43 secondary) administered vehicle chewable tablets. The dogs were 2 months to 15 years old and weighed 4.0 to 154.2 pounds. Of those dogs enrolled in the study, 173 primary dogs (104 treated and 69 control) were included in the effectiveness analysis, and 331 dogs (206 treated and 125 control) were included in the field safety assessment.

(3) Experimental Design:

Households were randomly assigned to receive either the imidacloprid or vehicle chewable tablet (Table 2). Within multi-dog households, eligible dogs were randomly assigned to serve as either primary or secondary dogs.

Table 2. Treatment Groups.

Body Weight (lbs)	Imidacloprid (mg/chewable tablet)	Vehicle (mg/chewable tablet)
4.0 to 22.0	7.5 mg	0 mg
22.1 to 110.0	37.5 mg	0 mg

(4) Drug Administration:

Based on body weight, dogs were administered the appropriate chewable tablet once daily for 14 days to deliver 0.3-1.9 mg imidacloprid/lb body weight. The control tablet was identical to the imidacloprid chewable tablet, but did not contain any active ingredient.

(5) Measurements and Observations:

Flea counts from the primary dogs were performed on Day 14. Complete blood count (CBC), serum chemistry analysis, serum thyroxine (T4), and complete urinalysis were assessed on Day 0 and Day 14 in primary dogs.

(6) Criteria for Success/Failure:

Ninety percent (90%) or greater reduction of live fleas at Day 14

d. Statistical Methods:

Flea effectiveness was calculated on the percent reduction in live flea counts in the treated group relative to the control group. Effectiveness was calculated as follows:

Percent Effectiveness = 100 * ((cc – ct)/cc)
cc = geometric mean number of live adult fleas in the control group
ct = geometric mean number of live adult fleas in the treated group

Since the effectiveness was greater than 90%, an analysis of variance (ANOVA) using the logarithm of the flea count (or count +1) was performed between the treated and control treatment groups. The model included treatment group as a fixed effect, and site and treatment by site interaction as random effects.

Clinical pathology variables were evaluated using an analysis of covariance (ANCOVA) with the pre-treatment value used as a covariate. The model included treatment group as a fixed effect, and site and treatment-by-site interaction as random effects.

e. Results:

The effectiveness analysis included 104 dogs in the treated group and 69 dogs in the control group. The geometric means of the live flea counts were 0.4 and 21.0 for the treated and control groups, respectively. The effectiveness was 98.2%. Table 3 summarizes the results.

Table 3. Results of the Effectiveness Analysis.

Treatment Group	# Dogs	Geometric Mean Flea Count	Percent Effectiveness	p value
Imidacloprid	104	0.4	98.2%	<0.0001
Control	69	21.0	n/a	<0.0001

f. Adverse Reactions:

The safety of imidacloprid was evaluated through review of adverse reactions and analysis of clinical laboratory variables (including complete blood count, serum chemistry profile, serum thyroxine, and urinalysis). Both primary and secondary dogs (n=331) were evaluated. No serious or life-threatening adverse reactions were noted in this study.

Ataxia was noted in one imidacloprid-treated dog for one day. Several cases of lethargy, vomiting, diarrhea/flatulence, and inappetence were also noted in treated and control animals, as shown in Table 4.

Table 4. Summary of Adverse Reactions.

Adverse Reaction	Imidacloprid N = 206 dogs (%)	Control N = 125 dogs (%)
Vomiting	8 (3.8%)	4 (3.2%)
Inappetence	6 (2.9%)	3 (2.4%)
Lethargy	4 (1.9%)	4 (3.2%)
Diarrhea, flatulence	3 (1.5%)	4 (3.2%)
Ataxia	1 (0.5%)	None

Clinical laboratory variables from pre-treatment to post-treatment were within the reference ranges for normal dog populations.

g. Conclusion:

Imidacloprid, when administered orally once daily for 14 days, is safe and effective for the treatment of cat flea (*C. felis*) infestations on dogs under field conditions. Vomiting was the most commonly reported adverse reaction.

2. Laboratory Dose Confirmation Study

a. Title:

Dose Confirmation of the Efficacy of Imidacloprid Soft Chewable Tablets Administered Orally to Dogs for the Treatment of Adult Cat Fleas (*Ctenocephalides felis*). Study Number P14-001.

b. Location:

BerTek Inc.
Greenbrier, AR

c. Study Design:

(1) Objective:

The objective of this study was to confirm the effectiveness of imidacloprid administered orally at a minimum dose of 0.34 mg/lb (0.75 mg/kg) to dogs infested with adult cat fleas (*C. felis*).

(2) Study Animals:

Forty-eight intact male and female mixed-breed and Beagle dogs, weighing between 18 to 22 pounds and aged 9 months to 7.5 years. Prior to enrollment, dogs demonstrated an ability to maintain viable populations of adult fleas.

(3) Experimental Design:

Dogs in Subgroups A and B received either imidacloprid or vehicle chewable tablets (control), respectively (Table 5). Dogs in Groups 1, 2, and 3 had flea counts performed at 8, 12, and 24 hours post-treatment, respectively.

Table 5. Treatment Groups.

Treatment Group	Treatment Assignment	Number and Gender of Animals
1A	Imidacloprid	4 females / 4 males
1B	Control	4 females / 4 males
2A	Imidacloprid	4 females / 4 males
2B	Control	4 females / 4 males
3A	Imidacloprid	4 females / 4 males
3B	Control	4 females / 4 males

(4) Drug Administration:

Dogs received either oral imidacloprid (7.5 mg) or the vehicle without the active ingredient once on Day 0.

(5) Measurements and Observations:

Dogs were observed 1, 2, and 4 hours (± 15 minutes) following treatment. Based on study group assignment, live flea counts were conducted at either 8, 12, or 24 hours following treatment on Day 0. The number of live fleas on each dog was determined using hand comb

counts. The entire body of each dog was systematically combed. Fleas and hair removed during combing were pulled out of the comb, and the living status of the fleas was noted. Live fleas, defined as either alive or moribund, were counted, and dead fleas were not counted. Dogs were combed until fleas were no longer found.

d. Statistical Methods:

For flea counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The fixed model analysis was used to analyze log-counts, with treatment group as a fixed effect.

e. Results:

(1) Flea Counts:

Results are summarized in Table 6. Adequate infestation, defined as a minimum of 50% flea retention (50 live fleas) in 6 out of 8 control dogs, was demonstrated at each time point (8, 12, and 24 hours), supporting model validity. When compared to the control group, effectiveness was 98.6, 99.9, and 100.0% at 8, 12, and 24 hours post-treatment, respectively. At each time point, the live flea counts for the imidacloprid group were significantly different from the control group ($p < 0.0001$).

Table 6. Summary of Flea Count Results.

Time (hr)	Treatment Group	Geometric Mean Flea Count	Percent Effectiveness	p-value
8	Imidacloprid	3.0	98.6%	<0.0001 ±
8	Control	85.1	N/A*	N/A
12	Imidacloprid	0.1	99.9%	<0.0001 ±
12	Control	89.8	N/A	N/A
24	Imidacloprid	0.0	100.0%	<0.0001 ±
24	Control	91.1	N/A	N/A

*N/A= not applicable
± Statistically significant at $p \leq 0.01$

f. Adverse Reactions:

One dog in the imidacloprid group vomited within 10 minutes after dosing.

g. Conclusions:

Imidacloprid administered orally to dogs was 100% effective against adult cat fleas (*C. felis*) infestations 24 hours after treatment.

3. Knockdown and Speed of Kill Effectiveness Study

a. Title:

Knockdown and Speed of Kill Effectiveness of Imidacloprid Soft Chewable Tablets for the Treatment of Adult Cat Fleas (*Ctenocephalides felis*) on Dogs. Study Number P14-006.

b. Location:

BerTek, Inc.
Greenbrier, AR

c. Study Design:

(1) Objective:

The objective of this study was to confirm the speed of kill effectiveness of imidacloprid administered orally at a minimum dose of 0.34 mg/lb (0.75 mg/kg) to dogs infested with adult cat fleas (*C. felis*).

(2) Study Animals:

Forty-eight intact male and female Beagles, Beagle crosses, and hound crosses, weighing between 14.3 to 37.1 pounds and aged 8 months to 8 years. Prior to enrollment, dogs demonstrated an ability to maintain viable populations of adult fleas.

(3) Experimental Design:

Dogs received either oral imidacloprid chewable tablets (treated group) or were sham-dosed (control group) once on Day 0 (Table 7). Dogs were subdivided into groups of 6 for flea count evaluation at one of four time points following treatment (0.5, 1, 4, or 24 hours).

Table 7. Treatment Groups.

Treatment Group	Treatment Assignment	Number and Gender of Animals
A	Imidacloprid	12 females / 12 males
B	Sham dose	12 females / 12 males

(4) Drug Administration:

Dogs in the treated group received either one 7.5 mg or one 37.5 mg imidacloprid chewable tablet according to the dosing table (Table 8). Dogs in the control group were sham-dosed.

Table 8. Dosing Table.

Body Weight (lbs)	Imidacloprid (mg/chewable tablet)	Dose Range (mg/lb)
4-22	7.5 mg	0.34-1.9
22.1-110	37.5 mg	0.34-1.7

(5) Measurements and Observations:

Based on study group assignment, live flea counts were conducted at either 0.5, 1, 4, or 24 hours following treatment on Day 0. The number of live fleas on each dog was determined using hand comb counts. The entire body of each dog was systematically combed. Fleas and hair removed during combing were pulled out of the comb, and the living status of the flea was noted. Live fleas, defined as either alive or moribund, were counted, and dead fleas were not counted. Dogs were combed until fleas were no longer found.

d. Statistical Methods:

For flea counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The fixed model analysis was used to analyze log-counts, with treatment group as a fixed effect.

e. Results:

Results are summarized in Table 9. Adequate infestation, defined as a minimum of 50% flea retention (50 live fleas) in all 6 control dogs, was achieved at each time point (0.5, 1, 4, and 24 hours). When compared to control, effectiveness was 96.6% and 99.9% at 4 and 24 hours post-treatment, respectively. The percent effectiveness was less than 90% at the 0.5 hour and 1 hour time points (Table 9). Statistical significance was demonstrated in the treated group compared to the control group at all time points except the 0.5 hour time point.

Table 9. Summary of Flea Count Results.

Time (hr)	Treatment Group	Geometric Mean Flea Count	Percent Effectiveness	p value
0.5	Imidacloprid	79.0	24.6%	0.2719
0.5	Control	94.3	N/A*	N/A
1	Imidacloprid	64.3	29.7%	0.0073±
1	Control	91.0	N/A	N/A
4	Imidacloprid	3.2	96.6%	<0.0001±
4	Control	85.8	N/A	N/A
24	Imidacloprid	0.2	99.9%	<0.0001±
24	Control	94.8	N/A	N/A

*N/A= not applicable
±Statistically significant at p≤0.01

f. Conclusion:

Imidacloprid starts killing fleas within 1 hour and demonstrated 96.6% effectiveness at 4 hours post-treatment.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study PAH-09-0029

1. Title:

Imidacloprid Soft Chew: A 6-Month Target Animal Safety Study in Beagle Puppies. Study Number PAH-09-0029.

2. Location:

MPI Research
Mattawan, MI

3. Study Design:

a. Objective:

To evaluate the safety of imidacloprid when administered orally to 10 week old Beagle puppies, once daily at 1.7, 5.1, or 8.5 mg/lb/day (0.9X, 2.7X and 4.5X, respectively, of the maximum exposure dose of 1.9 mg/lb/day) for 6 months.

b. Study Animals:

Thirty-two Beagles (16 males and 16 females) approximately ten weeks of age at the time of first administration were used in the study.

c. Experimental Design:

Table 10. Treatment Groups.

Treatment Group	Dose (mg/lb)	Number and Gender of Animals
1	0.0 mg/lb imidacloprid (0X)	4 females / 4 males
2	1.7 mg/lb imidacloprid (0.9X)	4 females / 4 males
3	5.1 mg/lb imidacloprid (2.7X)	4 females / 4 males
4	8.5mg/lb imidacloprid (4.5X)	4 females / 4 males

d. Drug Administration:

Imidacloprid chewable tablets were administered once daily by mouth for 182 days (6 months). The control dogs were sham-dosed.

e. Measurement and Observations:

Physical and neurologic examinations were conducted during acclimation, weekly during Weeks 1-4, then monthly through study end. Clinical pathology (hematology, serum chemistry, urinalysis, thyroid hormones) was evaluated on Day -4, then monthly during the study. Clinical observations were conducted twice daily throughout the study. Body weight was recorded three times weekly during acclimation (Days -15 to -1), three times during Week 1, twice during Week 2, then weekly from Week 3 through study end. Dry and wet food consumption were measured and recorded daily. At study end, gross necropsy and histopathology were performed, and organs weights were recorded.

4. Statistical Methods:

Continuous endpoints measured repeatedly 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. Baseline measurements were included as covariates. Continuous endpoints measured once were analyzed by analysis of variance. All statistical comparisons of main effects and two-way interactions were performed at the 0.10 level of significance; and the three-way interaction was performed at the 0.05 level of significance. Follow-up pairwise mean comparisons between the zero dose group and each non-zero dose group were performed, as necessary, using linear contrasts with significance level 0.10.

5. Results:

   There were no clinically-relevant, drug-related effects on physical examination, body weight, food consumption, clinical pathology, necropsy, or histopathology results.

6. Conclusion:

   Imidacloprid, administered orally once daily at 1.7, 5.1, or 8.5 mg/lb/day (0.9X, 2.7X and 4.5X, respectively, of the maximum exposure dose of 1.9 mg/lb/day) for 6 months, was well tolerated and did not produce clinically-relevant findings in Beagles, when dosing started at 10 weeks of age.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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 ADVANTUS:

Warnings:
Not for human use. Keep this and all drugs out of the reach of children and pets.

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 ADVANTUS, when used according to the label, is safe and effective for killing adult fleas and for the treatment of flea infestations on dogs and puppies 10 weeks of age and older and weighing 4 pounds of weight or greater.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use for laypeople.

B. Exclusivity

ADVANTUS, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of ADVANTUS.

C. Patent Information:

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