Date of Approval: August 20, 2012

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-277

COMFORTIS

Spinosad
Chewable Tablets
Dogs and Cats

The effect of the supplement is to 1) add an indication for use in cats: Kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month in cats and kittens 14 weeks of age and older, and two pounds of body weight or greater, and 2) add the 90 mg dose band for use of COMFORTIS in dogs.

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly & Co.

TABLE OF CONTENTS

I. GENERAL INFORMATION: 1

II. EFFECTIVENESS: 3

A. Dosage Characterization: 3
B. Substantial Evidence: 5

III. TARGET ANIMAL SAFETY: 18

A. Margin of Safety Study 025821: 18

IV. HUMAN FOOD SAFETY: 20

V. USER SAFETY: 20

VI. AGENCY CONCLUSIONS: 21

A. Marketing Status: 21
B. Exclusivity: 21
C. Supplemental Applications: 21
D. Patent Information: 21

I. GENERAL INFORMATION:

A. File Number:	NADA 141-277
B. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
C. Proprietary Name(s):	COMFORTIS
D. Established Name(s):	Spinosad
E. Pharmacological Category:	Antiparasitic
F. Dosage Form(s):	Chewable tablets
G. Amount of Active Ingredient(s):	Each tablet contains 90, 140, 270, 560, 810, or 1620 mg of spinosad.
H. How Supplied:	The product is available in six tablet sizes (90, 140, 270, 560, 810, or 1620 mg), formulated according to the weight of the dog or cat. Each tablet size is available in color-coded packages of 6 tablets each.
I. How Dispensed:	Rx

J. Dosage(s):

DOGS

COMFORTIS is given orally, once a month at the recommended minimum dosage of 13.5 mg/lb (30 mg/kg) body weight.

Dosage Schedule

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
3.3 to 4.9 lbs	90	One
5 to 10 lbs	140	One
10.1 to 20 lbs	270	One
20.1 to 40 lbs	560	One
40.1 to 60 lbs	810	One
60.1 to 120* lbs	1620	One

*Dogs over 120 lbs should be administered the appropriate combination of tablets.

CATS

COMFORTIS is given orally, once a month at the minimum dosage of 22.5 mg/lb (50 mg/kg) body weight.

Dosage Schedule

Body Weight	Spinosad Per Tablet (mg)	Tablets Administered
2 to 4 lbs	90	One
4.1 to 6 lbs	140	One
6.1 to 12 lbs	270	One
12.1 to 24* lbs	560	One

*Cats over 24 lbs should be administered the appropriate combination of tablets.

K. Route(s) of Administration:

Oral

L. Species/Class(es):

Dogs and Cats

M. Indication(s):

COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on dogs and puppies 14 weeks of age and older and 3.3 pounds of body weight or greater.
COMFORTIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*) for one month, on cats and kittens 14 weeks of age and older and two pounds of body weight or greater.

N. Effect(s) of Supplement: This supplement provides for the use of COMFORTIS in cats and for the addition of the 90 mg tablet size for use in dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

Dog

This supplemental approval does not change the previously approved dosage range. The Freedom of Information (FOI) Summary for the original approval of NADA 141-277, dated September 25, 2007, contains dosage characterization information for dogs.

Cat

The spinosad dosage selected for cats (50 mg/kg body weight administered once monthly after feeding) was based on a dose determination laboratory study and a fed/fasted pharmacokinetic study.

1. Dose Determination Study T9CUS090006

The dose determination study was conducted at Corapeake, NC, by L.R. Cruthers, Ph.D.

a. Study Design:
The study had five treatment groups with eight cats per group. Healthy cats were selected for the study and randomized to treatment group by their ability to maintain a flea infestation. Based on treatment group assignment, spinosad doses of 0 mg/kg (empty capsule), 35 mg/kg, 40 mg/kg, 45 mg/kg, or 50 mg/kg body weight (BW) were administered in gelatin capsules to cats on Study Day 0 only, after the cats had been fed. Each cat was infested with 100 unfed adult fleas on Study Days -1, 5, 12, 19, 28, and 35. Flea counts were conducted on Study Days 1, 7, 14, 21, 30, and 37, by personnel masked to treatment group.

b. Results:
The control group had geometric means (GM) of greater than 60 fleas at each flea count day. On Study Day 1, none of the cats in the spinosad treatment groups (35, 40, 45, or 50 mg/kg doses) had any fleas. On Study Day 30, the 35, 40, 45, and 50 mg/kg groups had 80.8%, 91.6%, 80.7%, and 97.3% reductions in geometric mean (GM) flea counts, respectively. On Study Day 37, the spinosad treatment groups each had less than 90% reductions in GM flea counts.

Adverse reactions included diarrhea, lethargy, decreased appetite, dehydration, vomiting, and loose stool in a 35 mg/kg group cat, and one episode of vomiting on Study Day 8 in a 50 mg/kg group cat.

c. Conclusion:
The study supported a spinosad dose of 50 mg/kg body weight given once monthly to fed cats.

2. Fed/Fasted Pharmacokinetic Study T9CUS090007

The fed/fasted pharmacokinetic study was conducted at Auxvasse, MO, by T.J. Madsen.

a. Study Design:
The study had two treatment groups (a fed group and a fasted group), with four male and four female adult cats per group, that were administered COMFORTIS. Food was removed overnight on Study Day -1. On Study Day 0, the fed group cats were offered approximately 25% of their daily ration, given 30 minutes to eat, and then dosed with at a target dose of 80 mg/kg BW spinosad. These cats were offered the remainder of their daily ration immediately following dose administration. On Study Day 0, the fasted group cats were fasted prior to dosing, dosed with COMFORTIS at a target dose of 80 mg/kg BW spinosad, and offered their daily ration of food two hours after dosing. Blood samples for plasma analysis were collected prior to dosing and at 0.5, 1, 2, 4, 8, 12, 24, 48, 120, 168, 240, 336, 408, 504, 576, and 672 hours (28 days) post-dosing. On Study Day 0, cats were monitored for vomiting for the first four hours post-dosing. Clinical observations were conducted twice daily.

b. Results:
The study demonstrated that systemic exposure of Spinosyns A and D[1], as measured by area under the curve of the plasma concentrations (AUC 0-inf) and maximum plasma concentration (Cmax), was substantially greater in fed than in fasted cats. See Tables 1 and 2, below.

Table 1: Mean Pharmacokinetic Parameters for Spinosyn A

Treatment Group	Tmax [a] Mean (SD)	Cmax/Dose [b] Mean (SD)	AUC/Dose [c] Mean (SD)	t½ [d] Mean (SD)
Fed Group	10 (3)	46 (14)	4489 (1182)	280 (74)
Fasted Group	6 (4)	11 (7)	781 (406)	193 (60)

[a] Tmax = time of maximum plasma concentration in hours.
SD = standard deviation.
[b] As actual doses varied, Cmax values were normalized to dose to allow for comparisons across treatment groups. Cmax values are in ng/mL for every mg/kg dose).
[c] As actual doses varied, AUC 0-inf (AUC) values were normalized to dose to allow for comparisons across treatment groups. AUC values are in hr×ng/mL for every mg/kg dose.
[d] t½ = time in hours for half of the quantity of drug to be metabolized or eliminated.

[1] Spinosad is composed of two isomers, Spinosyn A and Spinosyn D.

Table 2: Mean Pharmacokinetic Parameters for Spinosyn D

Treatment Group	Tmax [a] Mean (SD)	Cmax/Dose [b] Mean (SD)	AUC/Dose [c] Mean (SD)	t½ [d] Mean (SD)
Fed Group	10 (3)	12 (4)	1045 (321)	310 (113)
Fasted Group	6 (4)	2 (1)	98 (97)	184 (103)

[a] - [d] See footnotes to Table 1, above.

Adverse reactions included three episodes of vomiting and one episode of abnormal feces in the fed group; all occurred greater than 2.5 hours post- dosing.

c. Conclusion:
Cats should be administered COMFORTIS in the fed state for maximum absorption.

B. Substantial Evidence:

Dog

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-277, dated September 25, 2007, contains a summary of studies that demonstrate effectiveness of the drug for dogs.

Cat

1. Dose Confirmation Study T9CUS100016

a. Title:
Clinical Study (GCP): Dose Confirmation Laboratory Study of a Flavored Spinosad Tablet Administered Orally to Cats Experimentally Infested with Fleas (*Ctenocephalides felis*)

b. Investigator:
David R. Young, DVM, PhD, Turlock, CA

c. Study Design:
1. Objectives:
Confirm the dose of spinosad administered as a flavored tablet at the lower half (50-75 mg/kg) of the proposed label dose by evaluating the effectiveness in cats experimentally infested with adult fleas (*Ctenocephalides felis*) and document any post-treatment adverse events observed in the study cats.

2. Study Animals:
24 domestic cats (12 cats per treatment group)

3. Treatment Groups:

Table 3 Treatment Groups

Treatment Group	Dose	Tablet Treatments	Frequency / Duration	Number and Gender of Cat
1	0 mg/kg	Control (final oral dosage form without actives)	Once on Study Day 0	12 (7 M, 5 F)
2	50-75 mg/kg spinosad	COMFORTIS	Once on Study Day 0	12 (5 M, 7 F)

4. Drug Administration:
All treatments were administered orally. Food was removed overnight on the day prior to dosing. On Study Day 0, cats were offered approximately 25% of their ration and given 30 minutes to eat. Cats were dosed after consuming their food.

5. Measurements and Observations:
Each cat was infested with approximately 100 unfed adult fleas (*Ctenocephalides felis*) on Study Day -9. The twenty-four (24) cats that met the inclusion/exclusion criteria and had the highest pre-treatment live flea (*Ctenocephalides felis*) counts were included in a randomized complete block design with pre-treatment live flea counts used as a blocking factor. The Study Day -7 live flea counts were used to allocate cats to one of two treatment groups. The two treatment groups of 12 cats per group were orally dosed on Study Day 0. Each cat was infested with approximately 100 unfed adult fleas (*Ctenocephalides felis*) on Study Days -1, 5, 12, 19, 28, and 35. Individual cat live flea counts were performed on Study Days 1, 7, 14, 21, 30, and 37. Effectiveness against experimentally induced adult *Ctenocephalides felis* populations was determined by comparing post-treatment flea counts between the treated and control groups.

6. Statistical Methods:
Drug effectiveness was calculated as:

% Effectiveness = (P2 – P1)/P2 x 100

P1 = Geometric mean flea count for the treatment group
P2 = Geometric mean flea count for the control group

Log-transformed flea counts for the treatment and control groups were analyzed using a repeated measures linear model with fixed effects for treatment group, study day, and the treatment group-by-study day interaction. Contrasts were formed on the treatment group-by-study day interaction to allow comparison at different time points. If the normality

assumption was not met for the residuals from the repeated measures model, the non-parametric Wilcoxon rank sum test was used to evaluate the data, comparing each spinosad dose against control at each time point of interest. All statistical tests were two-tailed and conducted at alpha = 0.05.

d. Results:
COMFORTIS was 100% effective against *Ctenocephalides felis* on Study Day 1. The residual effectiveness based on geometric means was 99.8%, 99.6%, 95.8%, 90.8%, and 90.4% for Study Days 7, 14, 21, 30, and 37, respectively. The difference between the control and COMFORTIS groups was significant on all Study Days (Study Days 1, 7, 14, 21, 30, and 37; $p<0.0001$ on each day). See Table 4 below.

Table 4. Percent Effectiveness of COMFORTIS against *Ctenocephalides felis* Infestations on Cats

Study Day	1	7	14	21	30	37
Percent Effectiveness	100.0%	99.8%	99.6%	95.8%	90.8%	90.4%

e. Adverse Reactions:
Adverse reactions in the COMFORTIS-treated group consisted of two cases of vomiting after dosing. These adverse reactions were likely treatment related.

f. Conclusions:
COMFORTIS is ≥ 90% effective against induced *Ctenocephalides felis* infestations in cats for at least 30 days after dosing with 50-75 mg/kg, the lower half of the proposed dose range of 50-100 mg/kg.

2. Speed of Kill Study T9CUS100015

a. Title:
Clinical Study (GCP): Knockdown and Speed of Kill Effectiveness of Spinosad Tablets Administered Orally to Cats for the Treatment of Adult Cat Fleas (*Ctenocephalides felis*)

b. Investigator:
David R. Young, DVM, PhD
Turlock, CA

c. Study Design:
1. Objectives:
Confirm the knockdown and speed of kill effectiveness of spinosad administered as a flavored tablet to experimentally infested cats at a dosage of 50-100 mg/kg, for the treatment of the adult cat flea (Ctenocephalides felis) infestations on cats under laboratory conditions, and document any adverse reactions observed in the study cats.

2. Study Animals:
   60 domestic cats (6 cats per treatment group)

3. Treatment Groups:

Table 5. Treatment Groups

Treatment Group	Dose	Tablet Treatments	Hours Post-Treatment	Number and Gender of Cats
1	0 mg/kg	Control (final oral dosage form without actives)	0.5	6 (2 M, 4 F)
2	0 mg/kg	Control (final oral dosage form without actives)	2	6 (6 F)
3	0 mg/kg	Control (final oral dosage form without actives)	4	6 (1 M, 5 F)
4	0 mg/kg	Control (final oral dosage form without actives)	8	6 (3 M, 3 F)
5	0 mg/kg	Control (final oral dosage form without actives)	24	6 (3 M, 3 F)
6	50-100 mg/kg spinosad	COMFORTIS	0.5	6 (2 M, 4 F)
7	50-100 mg/kg spinosad	COMFORTIS	2	6 (3 M, 3 F)
8	50-100 mg/kg spinosad	COMFORTIS	4	6 (2 M, 4 F)
9	50-100 mg/kg spinosad	COMFORTIS	8	6 (2 M, 4 F)
10	50-100 mg/kg spinosad	COMFORTIS	24	6 (3 M, 3 F)

4. Drug Administration:
   All treatments were administered orally. Food was removed overnight on the day prior to dosing. On Study Day 0, cats were offered approximately 25% of their ration and given 30 minutes to eat. Cats were dosed after consuming their food.

5. Measurements and Observations:
   On Study Days -8 and -1, each cat was infested with approximately 100 newly emerged, unfed adult fleas (*Ctenocephalides felis*). Individual cat flea counts were performed approximately 24 to 48 hours post-infestation on Study Days -7, 0, and 1. The Study Day -7 pre-treatment live flea counts were used to allocate cats to the ten treatment groups. Ten treatment groups of six cats per group were orally dosed on Study Day 0. Five of the treatment groups (Groups 1-5) received control tablets (0 mg/kg); the remaining five treatment groups (Groups 6-10) received COMFORTIS at a dose of 50-100 mg/kg body weight. Post-dosing flea counts were conducted at approximately 0.5, 2, 4, 8, and 24 hours post-dose for Groups 1 and 6, 2 and 7, 3 and 8, 4 and 9, and 5 and 10, respectively. The Study Day 0 and Study Day 1 flea counts were used to evaluate the knockdown and speed of kill effectiveness in each of the treated groups compared to the respective control group.

6. Statistical Methods:
   Drug effectiveness was calculated as:

   % Effectiveness = (P2 – P1)/P2 x 100

   P1 = Geometric mean flea count for the treatment group
   P2 = Geometric mean flea count for the control group

   Log-transformed flea counts for the treatment and control groups were analyzed using a linear model with a fixed effect for treatment group. The treatment group effect defined in the analysis incorporated both the treatment and time aspects of interest (e.g. spinosad treated group with flea counts performed 4 hours post-dose). Contrasts were formed between the treated and control groups with flea counts performed at each observation time. If the normality assumption was not met for the residuals from the linear model, the non-parametric Wilcoxon rank sum test was used to evaluate the data at each time point of interest. All statistical tests were two-tailed and conducted at alpha = 0.05.

d. Results:
   COMFORTIS demonstrated 97.5% knockdown at 4 hours post- dosing. The differences in flea counts compared to the control group were statistically significant ($p \leq 0.05$) for four of the five COMFORTIS- treated groups (at 2, 4, 8, and 24 hours post dosing) using both parametric and non-parametric statistical testing. See Table 6 below.

Table 6. Geometric Mean Live Flea Counts and Percent Effectiveness at Times Post-Treatment

Treatment	0.5 Hr	2 Hr	4 Hr	8 Hr	24 Hr
Control	70.9	62.7	69.8	53.0	69.0
COMFORTIS (50-100 mg/kg)	59.0	4.6	1.7	1.6	0.0
% Effectiveness	16.8	92.7*	97.5*	96.9*	100.0*

*Statistically significant difference ($p \leq 0.05$) in flea counts between control and COMFORTIS-treated groups.

e. Adverse Reactions:
There were no adverse reactions in any treatment group.

f. Conclusions:
COMFORTIS begins killing fleas 30 minutes after dosing in a laboratory study using induced infestations and was ≥ 90% effective starting at 2 hours after dosing. By 24 hours, effectiveness was 100%.

3. Simulated Home Environment Study T9CUS100017

a. Title:
Clinical Study (GCP): Efficacy of Flavored Spinosad Tablets Administered Orally to Cats in a Simulated Home Environment for the Prevention of Cat Flea (*Ctenocephalides felis*) Infestations.

b. Investigator:
David R. Young, DVM, PhD
Turlock, CA

c. Study Design:
1. Objectives:
Confirm the effectiveness of spinosad administered as a flavored tablet at the lower half of the proposed label dose (50-75 mg/kg), for the prevention of cat flea (*Ctenocephalides felis*) infestations on cats under simulated home environment conditions, and document any post-treatment adverse events observed in the study cats.

2. Study Animals:
24 domestic feline (12 cats per treatment group)

3. Treatment Groups:

Table 7. Treatment Groups

Treatment Group	Dose	Tablet Treatments	Frequency/ Duration	Number and Gender of Cat
1	0 mg/kg	Control (final oral dosage form without actives)	Study Days 0, 30, and 60	12 (4 M, 8 F)
2	50-75 mg/kg spinosad	COMFORTIS	Study Days 0, 30, and 60	12 (3 M, 9 F)

4. Drug Administration:
   All treatments were administered orally. Food was removed overnight on the day prior to dosing. On each Study Day, cats were offered approximately 25% of their ration and given 30 minutes to eat. Cats were dosed after consuming their food.

5. Measurements and Observations:
   On Study Day -7, each cat was infested with approximately 100 newly emerged, unfed adult fleas (*Ctenocephalides felis*), and on Study Day -5 each cat was combed. The Study Day -5 pre-treatment live flea counts were used to allocate cats to the two treatment groups. On Study Day -1 all cats were combed to ensure all study cats were free of fleas prior to treatment on Study Day 0. On Study Days 1, 7, and 14, each cat was infested with approximately 100 unfed adult fleas. Two treatment groups of 12 cats per group were orally dosed on Study Days 0, 30, and 60. The control group (Group 1) received control tablets (0 mg/kg) while the treated group (Group 2) received COMFORTIS at a dose of 50-75 mg/kg body weight. Individual cat flea counts were performed on Study Days 3, 9, 16, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, and 95. Up to 300 live fleas were replaced on each cat after the comb count was complete. Fleas were not replaced on Study Day 95. To encourage and maintain flea production and provide a suitable simulated home environment for flea larval development throughout the study, the carpeted area in each solid-sided and solid-flooring cage was sprinkled with similar amounts of larval flea growth media (dried blood, yeast, etc.) weekly throughout the study. The treatment phase of the study began on Study Day 0 and continued until the time of study completion on Study Day 95.

   The primary variable evaluated was effectiveness against *C. felis*. Post-treatment flea counts of COMFORTIS treated cats compared to the control group were used to assess effectiveness. Effectiveness of the treatment for each post-treatment time point evaluated was claimed if the treatment group had at least 90% effectiveness compared to the control group, and the treatment group demonstrated a statistically significant ($p<0.05$, two-sided)

decrease in the number of live fleas compared to the control group.

6. Statistical Methods:
Drug effectiveness was calculated as:

% Effectiveness = (P2 – P1)/P2 x 100

P1 = Geometric mean flea count for the treatment group
P2 = Geometric mean flea count for the control group

Log-transformed flea counts for the treatment and control groups were analyzed using a repeated measures linear model with fixed effects for treatment group, study day, and the treatment group-by-study day interaction. Contrasts were formed on the treatment group-by-study day interaction to allow comparison at different time points. If the normality assumption was not met for the residuals from the repeated measures model, the non-parametric Wilcoxon rank sum test was used to evaluate the data, comparing each spinosad dose against control at each time point of interest. All statistical tests were two-tailed and conducted at alpha = 0.05.

d. Results:
COMFORTIS demonstrated 100% effectiveness at each post- treatment time point.

e. Adverse Reactions:
There were no adverse reactions in the COMFORTIS-treated group.

f. Conclusions:
COMFORTIS is effective in preventing flea infestations in the simulated home environment when dosed orally at 50-75 mg/kg, the lower half of the proposed dosage range of 50-100 mg/kg.

4. Field Study T9CUS100002

a. Study Title:
Clinical Study (GCP): A Clinical Safety and Effectiveness Evaluation of Spinosad Tablets in Client-Owned Cats

b. Investigators:
Lynn Buzhardt, DVM, Zachary, LA
William Campaigne, DVM, Seguin, TX
Terry Clekis, DVM, Bradenton, FL
Deborah Edwards, DVM, Largo, FL
Samuel Geller, VMD, Quakertown, PA
Adele Mays, DVM, Knoxville, TN
Roger Sifferman, DVM, Springfield, MO
Casey Thomas, DVM, Junction City, KS

c. Study Design:

1. Study Objectives:
   - To evaluate the effectiveness of COMFORTIS against naturally occurring flea infestations in client-owned cats when administered monthly for three consecutive months
   - To evaluate the effect of treatment with COMFORTIS on flea allergy dermatitis (FAD) in client-owned cats
   - To evaluate the safety of COMFORTIS when administered for three consecutive months in client-owned cats

2. Study Animals:
   The study enrolled 212 client-owned domestic cats, indoor and outdoor, mixed breed and purebred, male and female, reproductively intact and neutered, 14 weeks of age and older, and 2 lb (0.9 kg) body weight or greater. The study excluded pregnant or lactating cats, and cats intended for breeding during the study.

   The study allowed up to three cats per household. At least one cat per household had to have five or more fleas. Each household had one primary cat, a cat with at least five fleas. In multi-cat households, primary cats were randomly selected at enrollment from the cats in that household with at least five fleas. Households with dogs were not allowed to participate unless there were three or fewer outdoor-only dogs that did not co-mingle with the cats, and the dogs were on an approved flea-control product for the duration of the study.

3. Treatment Groups:
   Households were randomized 2:1 to the COMFORTIS or selamectin treatment groups. Regardless of flea burden, all cats in a household (primary and secondary) had to participate in the study and they received the same treatment product.

   The study randomized 80 households (140 cats) to treatment with COMFORTIS and 40 households (72 cats) to treatment with selamectin.

   Table 8: Treatment Groups

Treatment Group	Dose, Route, and Frequency
COMFORTIS Chewable Tablets	50-100 mg/kg spinosad orally, once monthly for 3 consecutive months
Selamectin: REVOLUTION Topical Solution	≥ 6 mg/kg selamectin topically, per label dose bands, once monthly for 3 consecutive months

4. Drug Administration:
   Owners dosed their cats (primary and secondary) once monthly at home, within two days after the Study Day -1 and Study Day 30 clinic visits, and on Study Day 60. Owners administered COMFORTIS after offering food to their cats.

5. Measurements and Observations:
   All cats that received at least one dose of COMFORTIS or selamectin were assessed for safety. Primary cats were assessed for effectiveness.

   Clinic personnel, masked to treatment, performed flea counts on all cats on Study Day -1, and on the primary cats on Study Days 30 and 90.

   The investigator, masked to treatment, performed FAD scoring on the primary cats on Study Days -1, 30, and 90. For the each of the six FAD criteria (pruritus, papules, erythema, alopecia, scaling, and dermatitis/pyoderma), the investigator recorded a score of 0 = absent, 1 = mild, 2 = moderate, or 3 = severe.

   Owners reported the successful method of administration of COMFORTIS for each cat at each monthly treatment.

   Physical examinations and body weight measurements were conducted on Study Days -1, 30, and 90 for all cats. Cats expected to gain weight were also weighed just before the Study Day 60 dosing. Hematology and serum chemistry were collected on Study Days -1 and 90 for all cats. Owner observations were recorded post-dosing.

6. Statistical Methods:
   A parallel-arm study design was used comparing COMFORTIS to selamectin. The primary cat from each household was the experimental unit. The reduction in flea burden was calculated using log-transformed flea counts (Log[count+1]) analyzed using a repeated measures model which included treatment, time, and the treatment-by-time interaction effects. The non-inferiority of COMFORTIS is achieved if the reduction in flea count is greater than or equal to 90%, and the decrease in Least Squares (LS) mean flea count at Study Day 90 is statistically significant compared to Study Day -1 for each of the COMFORTIS and selamectin groups.

   Improvement in the signs of FAD for an individual cat was defined as a reduction in severity of the FAD clinical sign from Study Day -1 to Study Day 90. In addition, the change from pre- to post-treatment FAD scores was analyzed using a weighted average of the percentage of cats showing improvement across the signs of FAD. The weighting used for this calculation was the number of cats with the particular sign prior to treatment.

d. Results:
   Of the 212 cats enrolled, 211 (139 COMFORTIS and 72 selamectin) received at least one treatment, and were evaluated for safety. Of the 120 primary cats (households) enrolled, 102 primary cats (68 COMFORTIS and 34 selamectin) were evaluated for effectiveness.

Primary cats were excluded from the effectiveness data set because of owner non-compliance (e.g., failure to return for final visit, use of prohibited concurrent medication), non-conformance to eligibility criteria, and one death considered unrelated to treatment. Primary cats from sites that enrolled insufficient numbers of cases were also excluded from the effectiveness evaluation.

1. Treatment of Flea Infestations:
   Both treatment groups showed greater than 90% effectiveness in the reduction of flea counts at Study Day 90. The 95% confidence interval for the difference (Day 1 – Day X) was calculated using LS Means, and did not include zero. Thus, there was a significant reduction in the flea counts. See Table 9.

Table 9: Percent Reduction in Geometric Mean Flea Count Relative to Study Day -1 (Geometric Mean Flea Count)

Treatment group	Study Day -1	Study Day 30	Study Day 90
COMFORTIS (n = 68)	N/A (34.9)	97.6% (0.8)	99.3% (0.2)
Selamectin (n = 34)	N/A (53.3)	88.8% (6.0)	97.7% (1.2)

2. Flea Allergic Dermatitis:
   The primary cats with signs of FAD at Study Day-1 in the COMFORTIS group showed a greater or equal percentage of improvement in each of the FAD criteria compared to the selamectin group. See Tables 10a and 10b. The improvement across signs of FAD in the COMFORTIS group by weighted average was 94.2% compared to 80.0% in the selamectin group.

Table 10a: Summary of Cats with Improved FAD Scores, COMFORTIS Group (n=68)

FAD Signs [a]	Number of Cats with Score > 0 at Study Day -1	Number of Cats with Improved Score at Study Day 90	Percent of Cats with Improved Scores
Pruritus	56	55	98.2%
Papules	2	2	100.0%
Erythema	18	16	88.9%
Alopecia	22	21	95.5%
Scaling	13	10	76.9%
Dermatitis/ Pyoderma	9	9	100.0%

[a] Each FAD Sign was scored as Absent = 0, Mild = 1, Moderate = 2, or Severe = 3

Table 10b: Summary of Cats with Improved FAD Scores, Selamectin Group (n=34)

FAD Signs [a]	Number of Cats with Score > 0 at Study Day -1	Number of Cats with Improved Score at Study Day 90	Percent of Cats with Improved Scores
Pruritus	28	23	82.1%
Papules	1	1	100.0%
Erythema	9	8	88.9%
Alopecia	9	6	66.7%
Scaling	8	5	62.5%
Dermatitis/ Pyoderma	5	5	100.0%

[a] Each FAD Sign was scored as Absent = 0, Mild = 1, Moderate = 2, or Severe = 3

3. Tablet Consumption:
   Over the duration of the study, owners reported the consumption of the COMFORTIS doses by their cats in the following order: administered (pilled) like other tablet medications (59.6%), offered in or on food (27.3%), or consumed voluntarily (11.2%) when offered free choice (by hand, from the floor, or in a bowl). The remaining 1.9% of tablets were lost or damaged and a new tablet was subsequently dosed in one of the ways listed above. The percent of doses that were pilled increased with repeated doses, from 47.3% for the first monthly dose to 70.7% for the third monthly dose.

4. Clinical Pathology:
   Hematology and serum chemistry values were compared from the enrollment visit to the exit visit and were unremarkable, showing no consistent clinically significant trends.

5. Body Weight:
   Adult cats in the COMFORTIS group gained less weight than adult cats in the selamectin group. Five adult cats in the COMFORTIS group lost over 10% of their body weight in the time difference between the Study Day -1 and Study Day 90 visits. None of the cats in the selamectin group lost over 10% body weight.

6. Concurrent Medication:
   COMFORTIS was administered safely in conjunction with other frequently used veterinary products, including tapeworm anthelmintics, antibiotics, and an approved heartworm preventative containing ivermectin. Two cats that received extra-label topical otic ivermectin on Study Day -1 of the field study developed lethargy on Study Day 1 after COMFORTIS administration on Study Day 0.

e. Adverse Reactions:
   No serious adverse reactions were attributed to COMFORTIS or selamectin. The most commonly reported adverse reaction was vomiting. Adverse reactions that occurred at an incidence of greater than 1% within any of the three months of observations (dosing intervals) are presented in Table 11.

Table 11: Percent of Cats with Common Adverse Events by Dosing Interval

Adverse Reaction	Month 1 COMFORTIS (n=139)	Month 1 Selamectin (n=72)	Month 2 COMFORTIS (n=135)	Month 2 Selamectin (n=69)	Month 3 COMFORTIS (n=132)	Month 3 Selamectin (n=67)
Vomiting	14.4	1.4	14.8	1.4	13.6	4.5
Lethargy	3.6	0.0	0.7	0.0	1.5	1.5
Anorexia	2.2	0.0	0.7	0.0	2.3	1.5
Weight Loss	1.4	0.0	0.0	0.0	3.0	0.0
Diarrhea	1.4	1.4	0.7	2.9	2.3	1.5

Over the 3-month (3-dose) study, vomiting occurred on the day of or the day after at least one dose in 28.1% (39/139) of the cats treated with COMFORTIS and in 2.8% (2/72) of the cats treated with selamectin. Three of the 139 cats treated with COMFORTIS vomited on the day of or the day after all three doses.

f. Conclusions:
At a dose range of 50-100 mg/kg spinosad, administered orally once monthly for three consecutive months, COMFORTIS was effective against naturally occurring flea infestations in client-owned cats. Cats with pre-existing signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyoderma, and pruritus as a result of eliminating the fleas. No serious adverse reactions were attributed to COMFORTIS. Vomiting was the most commonly reported adverse reaction. Lethargy, anorexia, weight loss, and diarrhea were also reported in over 1% of client-owned cats on COMFORTIS.

The safety and effectiveness of COMFORTIS was corroborated by results from a field study in client-owned cats in Europe (Study T9CDE100004).

5. Field Study T9CDE100004

"A European Multi-Centered Clinical Study to Evaluate the Efficacy and Safety of Spinosad Tablets in Client-Owned Cats Naturally Infested with Fleas"

The 60-day study was conducted at multiple sites in Germany and Italy. The 263 cats (179 COMFORTIS and 84 selamectin) enrolled in the study were dosed with COMFORTIS or selamectin on Study Days 0 and 30. Flea counts and flea allergic dermatitis (FAD) scoring were conducted on Study Days 14, 30, and 60. The COMFORTIS and selamectin groups had baseline geometric mean flea counts of 12 and 10.7, respectively. Both groups had greater than 90% reductions in flea counts at Study Days 14, 30, and 60 compared to baseline. The improvement in clinical signs of FAD in the COMFORTIS group at Study Day 60 in the EU field study was similar to results in the COMFORTIS group at Study Day 90 in the U.S. field study. Similar to the U.S. field study, the most common adverse reactions in the EU field study were vomiting and diarrhea, and the majority of these adverse reactions occurred on the day of or the day after dosing with COMFORTIS.

III. TARGET ANIMAL SAFETY:

Dog

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-277, dated September 25, 2007, contains a summary of target animal safety studies for dogs.

Cat

A. Margin of Safety Study 025821:

1. Study Title:

   Non-Clinical Laboratory Study: A Margin of Safety Study of Spinosad Administered Orally to Cats Starting at 14 Weeks of Age

2. Investigator:

   Michael C. Savides, PhD, Concord, OH

3. Study Design

   a. Study Objective:
   Evaluate the safety of COMFORTIS when administered orally to 14-week old kittens at 1X, 3X, and 5X the upper half (75-100 mg/kg) of the therapeutic dose band for six monthly dosing intervals 28 days apart.

   b. Study Animals:
   32 domestic cats (8 cats per treatment group)

   c. Treatment Groups:
   Table 12: Tablets Dosed (Control or COMFORTIS) [a]

Treatment Group	Study Day 0 [b]	Study Day 1	Study Day 2	Study Day 3	Study Day 4
Control	C	C	C	C	C
1X	C	C	C	C	S
3X	C	C	S	S	S
5X	S	S	S	S	S

[a] C= Control (final oral dosage form without actives) tablet dosed, S=COMFORTIS dosed at 1X the upper half of the therapeutic dose band (75-100 mg/kg).

[b] Dose interval 1 is shown. The same 5 day dosing schedule was followed in 28 day intervals for the second through the sixth dose. In the 3X and

5X groups, the spinosad dose was divided and administered over sequential days to obtain desired systemic exposures of the drug.

d. Drug Administration:
All treatments were administered orally. Food was removed overnight on the day prior to dosing. On each dosing day, cats were offered approximately 25% of their ration and given 30 minutes to eat. Cats were dosed after consuming their food.

e. Measurements and Observations:
All cats were observed at least twice daily throughout the duration of the study. A complete physical examination was conducted on all cats by a staff veterinarian on Study Days -3 and 165. Body weights for all cats were measured and recorded twice during acclimation and then every other week throughout the study. Clinical pathology (hematology and clinical chemistry) evaluations were conducted on all cats on Study Days -5, 81, and 165. Fecal examinations were performed on Study Days -5, -4, 17, 28, 81, and 165. Urinalysis evaluations were conducted on all cats on Study Days -5 or -4, 81, and 165. Blood samples were also collected for determination of Spinosyn A and Spinosyn D plasma concentrations on Study Days -6, 5, 11, 18, 33, 39, 46, 61, 67, 74, 89, 95, 102, 117, 123, 130, 145, 151, and 158. Necropsy examinations and organ weight determination were performed on Study Day 168. Histopathologic examination was performed on tissues from all cats.

f. Statistical Methods:
Endpoints measured multiple times post-treatment were analyzed by repeated measures mixed-effects model including fixed effects for treatment, time, sex; the two-way interactions between treatment, time and sex; and the three-way interaction treatment×time×sex. The average pretreatment value or, in the case of body weights, the last available pretreatment value was included as a covariate. A variety of covariance structures were fitted with the minimum Akaike Information Criterion used to select the final structure for the model. Single post-dose measurement endpoints were analyzed using a mixed-effect linear analysis of variance (ANOVA) model with fixed effects for treatment, sex, and the treatment by sex interaction. Gender-specific organ weights (testes and ovaries) were analyzed with an ANOVA including a fixed-effect term for treatment only.

4. Results:

There were no deaths during the course of the study. Vomiting was the most common clinical observation associated with the administration of COMFORTIS. Vomiting was observed across all groups, but was seen with greater frequency in cats in the groups administered COMFORTIS; it did not increase with increasing doses. All of the occasions of vomiting in 1X and 3X treatment groups were on days that the cats received the test article, but none of the cats in the 5X treatment group vomited on any of the days of dosing with test article. Loose stool was observed in cats in all but the 3X group.

Food consumption was decreased in the 5X female cats. No test article-related changes in hematology values were seen at any of the intervals of analysis. Minor elevations were seen in the alanine aminotransferase (ALT), aspartate aminotransferase (AST), and cholesterol values in the clinical chemistry but were not associated with any clinical signs.

Hepatocellular hypertrophy and vacuolation of the liver, and vacuolation of the lung and adrenal gland were noted in cats in the 3X and 5X groups. One 1X cat also had vacuolated macrophages in the lung. These findings are consistent with phospholipidosis.

One cat in the 3X group had an enlarged thyroid/parathyroid gland found at necropsy. Higher liver weights occurred in cats in the 3X and 5X groups that correlated with hepatocellular vacuolation and hypertrophy. There was no indication of any detrimental effects based on clinical chemistries and anatomical changes.

Spinosyn A and Spinosyn D plasma concentrations increased throughout the study. The plasma concentrations demonstrated that exposures in cats in the 3X and 5X treatment groups were more than dose proportional to exposures in cats in the 1X treatment group.

5. Conclusions:

The oral administration of COMFORTIS at 1X, 3X, and 5X the upper half of the therapeutic dose band once monthly for six dosing intervals in cats was well tolerated in this study. Plasma concentrations of Spinosyns A and D indicate that exposures in cats in the 3X and 5X treatment groups were more than dose proportional to exposures in cats in the 1X treatment group. Clinical signs related to the administration of COMFORTIS include: decreased food consumption, vomiting, loose stool, and phospholipidosis (vacuolation) of the liver, lung, and adrenal gland. The long term effects of phospholipidosis are unknown.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs 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 COMFORTIS:

Human Warnings are provided on the product label as follows: "Not for human use. Keep this and all drugs out of the reach of children."

The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the

MSDS for this product call 1-888-545-5973.

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 COMFORTIS, when used according to the label, is safe and effective for killing fleas and for the treatment and prevention of flea infestations.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to monitor for and respond to adverse reactions.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the new species for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA required 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.