CAPSTAR™ (nitenpyram) Tablets

For the treatment of flea infestations on dogs, puppies, cats and kittens four weeks of age and older and 2 of pounds body weight or greater

NADA 141 - 175

Novartis Animal Health US, Inc.

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Freedom of Information Summary

I. GENERAL INFORMATION

NADA Number: 141-175

Sponsor: Novartis Animal Health US, Inc.
Post Office Box 26402
Greensboro, NC 27404-6402

Generic Name of Drug: Nitenpyram

Trade Name: CAPSTAR™

Marketing Status: Over-the-Counter (OTC)

II. INDICATIONS FOR USE

CAPSTAR Tablets are for the treatment of flea infestations on dogs, puppies, cats and kittens four weeks of age and 2 pounds of body weight or greater.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

CAPSTAR Tablets should be administered orally, at a minimum dosage rate of 1.0 mg/kg (0.45 mg/lb) body weight, according to the Recommended Dosage Schedule below. **Weigh your pet prior to administration to ensure proper dosage.** Do not administer to pets under 2 pounds. CAPSTAR may be used as needed, as often as once per day, whenever you see fleas on your pet.

Table III.1 – Recommended Dosage Schedule

Species	Body Weight	Dose	Amount of Nitenpyram per Tablet
Dog or Cat	2 - 25 lbs.	One tablet	11.4 mg
Dog	25.1 - 125 lbs	One tablet	57 mg

IV. EFFECTIVENESS STUDIES FOR CATS

A. DOSAGE CHARACTERIZATION

Dose Titration to Determine Effectiveness of Nitenpyram in Cats Against Fleas

Purpose: To determine the effectiveness of nitenpyram against adult fleas when administered orally to cats.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: Mark S. Holbert

Study Location: Stillmeadow, Inc
Sugar Land, TX

Animals: Sixty domestic shorthaired cats (30 males and 30 females), ≥6 months of age except for three cats that were less than 6 months.

Dosage Groups: The cats were placed into six groups of five males and five females per group as shown in Table IV.1:

Table IV.1 - Dosage groups for nitenpyram cat dose titration

Group	Dosage (mg/kg)
1	untreated
2	0.025
3	0.05
4	0.1
5	0.2
6	0.4

Route of Administration: Oral

Frequency of Treatment: Single Dose

Controls: Untreated

Study Design: Cats were experimentally infested with 100 cat fleas on Day –1. Fleas were removed from all cats with a flea comb 24 hours after dosing (Day 1).

Results: Table IV.2 lists the number of live fleas collected from the cats and the effectiveness determination for each treatment group compared to the control group.

Table IV.2 - Dose titration results for nitenpyram in cats

Group	Dosage (mg/kg)	Number of Live Fleas	% Effectiveness
1	untreated	55.0	NA
2	0.025	6.8	87.6
3	0.05	0.2	99.6
4	0.1	0.1	99.8
5	0.2	0.0	100
6	0.4	0.0	100

Conclusions: Nitenpyram administered orally at doses ranging from 0.05 mg/kg to 0.4 mg/kg was effective for the treatment of flea infestations on cats as determined by the number of live fleas 24 hours after treatment.

Although the highest dose tested in this study was 0.4 mg/kg, the dose selected for further study was 1.0 mg/kg. The decision to increase the dose was based on the results of another pilot study conducted in dogs. The dog study showed that some of the fleas that had fallen off dogs treated at 0.2 and 0.4 mg/kg were still alive 24 hours after treatment. The minimum dose needed to ensure dead fleas on dogs was 1.0 mg/kg. Since safety is not a concern at these doses, the cat dose was also increased.

Details of the dog study, "Duration of Effectiveness of Nitenpyram Used on Dogs With Fleas" are presented on page 16.

B. DOSAGE CONFIRMATION

1) Confirmation of an Effective Dose of Nitenpyram Flavored Tablets for the Removal of Adult *Ctenocephalides felis* Fleas on Cats

Purpose: To confirm that the recommended use rate of nitenpyram is effective for the treatment of flea infestations on cats.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: Suzanne Craig

Study Location: Stillmeadow, Inc.
Sugar Land, TX

Animals: Ten mixed breed cats (5 males and 5 females), ≥6 months of age

Dosage Groups: Crossover design - Day 0 each cat received placebo and on Day 7 each received an 11.4 mg tablet, according to the recommended dosage schedule.

Route of Administration: Oral

Frequency of Treatment: Single Dose

Controls: Placebo

Study Design: Cats were experimentally infested with 100 cat fleas on Day -1 and Day 6. Placebo was administered on Day 0 and test article was administered on Day 7. At approximately 4 - 6 hours after treatment, each animal was combed and the cage pans examined. The number of live, dead, and moribund fleas on the animal and in the cage pan was counted and recorded. For each treatment, the total number of dead and moribund fleas on each animal was compared to the total number of fleas (including live fleas). The percentage of dead and moribund fleas was calculated.

Results: After the placebo treatment, <9% of fleas on cats were dead or moribund. After treatment with the test article, >90% of fleas on cats were dead or moribund by 4-6 hours after dosing.

Conclusions: The data confirmed that nitenpyram administered according to the recommended dosage schedule (minimum dose of 1.0 mg/kg) was effective for the treatment of flea infestations on cats.

2) Behavior of Moribund Fleas (*Ctenocephalides felis)* Affected by Nitenpyram after an Oral Application in Cats

Purpose: To determine the viability of moribund fleas from cats treated with oral nitenpyram according to the recommended dosage schedule.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: C. Bielmann

Study Location: Novartis Centre de Recherche
Sante Animale SA
Ch-1566
St-Aubin, Switzerland

Animals: Twelve cats (6 female and 6 males), ≥ 2 years of age

Dosage Groups: The cats were assigned to one of 4 groups as shown in Table IV.3.

Table IV.3 –Treatment groups for flea viability study

Group	Treatment	Infested
1	Nitenpyram*	100 fleas
2	None	100 fleas
3	None	None
4	None	None

*Each cat dosed with 1-11.4 mg tablet (1X), according to the recommended dosage schedule

Route of Administration: Oral

Frequency of Treatment: Single Dose

Controls: Untreated

Study Design: Cats in Groups 1 and 2 were infested with 100 fleas each. Two hours after treatment moribund fleas were collected from Group 1 cats and placed on carpets in cages containing untreated sentinel cats (Group 3). Fleas were removed from Group 2 cats and placed on carpets in cages containing untreated sentinel cats (Group 4). Viability of fleas was measured by the ability of fleas in Groups 3 and 4 to reinfest sentinel cats.

Results: *Flea Counts:* Percent efficacy was calculated using Abbott's formula.

(mean # of fleas on control cats) – (mean # of fleas on treated cats) / (mean #of fleas on control cats) x 100 = % efficacy.

Nitenpyram showed an average efficacy of 96% at 2 hours after treatment.

Flea Viability: Of the 99 moribund fleas deposited on the carpets of the Group 3 cats, only 1 live flea was found on a sentinel cat after 48 hours. Of the 100 live fleas deposited on the carpets of the Group 4 cats, 67 live fleas were found on the sentinel cats after 48 hours.

Conclusions: Fleas that are moribund due to exposure to the recommended dose of nitenpyram do not recover and reinfest cats.

3) The Rate of Knockdown of Fleas from Cats Treated with Nitenpyram

Purpose: The primary objective was to demonstrate and quantify the rate of knockdown of fleas on nitenpyram-treated cats. Secondarily, the impact of flea feeding behavior on treated and untreated cats was investigated.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: R. H. Mahoney

Study Location: Novartis Animal Health Australia Pty. Limited
R & D Centre
Yarrandoo
245 Western Road
Kemps Creek NSW 2171 Australia

Animals: The study used 14 adult mixed breed cats (7 females and 7 males)

Dosage Groups: The cats were divided into 4 groups of 3 and 1 group of 2 based on weight and gender. The study used a 3-phase crossover design. The cats were either treated in the morning or evening with the recommended dosage of nitenpyram or were untreated and were either infested with 100 fleas 24 hours prior to the test period or were not infested.

Route of Administration: Oral

Controls: Untreated

Parameters Evaluated: *Time to Knockdown:* At 0.5, 1, 2, 3, and 8 hours after treatment, fleas that fell from the cats were removed from the cages and counted. After 8 hours each cat was combed to remove any remaining live fleas.

Grooming Behavior: Scratching or grooming behavior was evaluated by videotaping the cats and comparing the activity of treated and control animals.

Results: *Time to Knockdown:* Percent knockdown was calculated. The results are presented in Table IV.4.

Table IV.4 – Cumulative percentage knockdown of fleas from cats treated with nitenpyram

Time Post-Treatment (Hours)	Cumulative % Knockdown
0.5	3.0
1.0	16.6
2.0	40.3
3.0	64.0
8.0	97.7

Grooming Behavior: Cats showed the most grooming behavior when infested with fleas and treated with nitenpyram. Treatment without infestation did not cause an increase in this behavior.

Conclusions: When cats were given a single oral dose of 11.4 mg nitenpyram, the product began working within 30 minutes of administration. By 8 hours post-treatment, 97.7 % of fleas had been knocked down. Nitenpyram treatment alone did not cause any behavior changes in cats; however, flea-infested cats showed a temporary increase in scratching and grooming behavior following treatment with nitenpyram.

C. CLINICAL FIELD STUDY

Controlled Clinical Study of Nitenpyram Flavored Tablets for the Removal of Fleas on Cats

Purpose: To demonstrate the safety and effectiveness of nitenpyram for the treatment of flea infestations on cats.

Type of Study: Multi-centered, double-blinded, placebo-controlled, clinical study

Investigator/Study Location: The study locations are listed in Table IV.5.

Table IV.5 – Sites for nitenpyram cat clinical study

Investigator Name	Institution	City	State
Dr. Mildred Bass	Village Veterinary Clinic	Farragut	TN
Dr. Gary H. Brotze	Creek View Veterinary Clinic	New Braunfels	TX
Dr. Bill Campaigne	Seguin Animal Hospital	Seguin	TX
Dr. Kathy Haigh	Haigh Veterinary Clinic	Shelton	WA
Dr. Jim Harris	Palmetto Animal Hospital	Florence	SC
Dr. Richard Johnson	Broadway Animal Hospital	El Cajon	CA
Dr. Dan McIlhany	Towne North Animal Hospital	San Antonio	TX
Dr. Gary Olson	Shelton Veterinary Clinic	Shelton	WA
Dr. Ann Parker	Hope Mills Road Animal Hospital	Fayetteville	NC

Investigator Name	Institution	City	State
Dr. Jim Raab	Tri-County Animal Hospital	Fort Pierce	FL
Dr. Roger Sifferman	Bradford Park Veterinary Hospital	Springfield	MO

Animals: One hundred fifty-seven naturally infested cats, weighing 2 lbs or greater and 4 weeks of age or older, were enrolled in the study. The study population, distributed by age and weight, is presented in Table IV.7 below.

Dosage Groups: The cats were placed into 2 groups: nitenpyram and placebo. The distribution among treatment groups is provided in Table IV.6.

Table IV.6 – Study population by treatment group and visit

Treatment Group	Visit 1	Visit 2
Nitenpyram	105	59
Placebo	52	46
Total	157	105

Table IV.7 – Study population by treatment group, age and weight

	Nitenpyram	Placebo
1-12 months	26	20
>1-5 years	50	20
>5-10 years	15	8
>10 years	14	4
2-10 lbs	73	36
>10-25	32	16

Dosage: Nitenpyram was administered orally once a day according to the recommended dosage schedule (minimum dose of 1.0 mg/kg) for a maximum of 16 daily treatments.

Controls: Placebo

Parameters Evaluated: Effectiveness was evaluated during two visits 7 to 14 days apart. The tablet was administered by the investigator at each of these visits. Dead, moribund, and live fleas were counted 4-6 hours after treatment.

Results: *Effectiveness:* Within 6 hours of initial administration, the nitenpyram group showed an average 98.4% dead and moribund fleas, while the placebo group had 5.7% dead and moribund fleas. At the second visit, the nitenpyram group had an average 99.9% dead and moribund fleas within 6 hours of administration, compared to 3.4% for the placebo group.

Safety: There were a variety of adverse events reported during the trial. There was no evidence that any of the reported adverse events were drug-related.

Conclusions: The data demonstrate that nitenpyram administered orally according to the recommended dosage schedule (minimum dose of 1.0 mg/kg) is safe and effective for the treatment of flea infestations on cats 4 weeks of age and older and 2 lbs body weight or greater.

D. BIOEQUIVALENCE STUDY

Blood Level Bioequivalence in Cats of 11.4 mg Nitenpyram Swallow Tablets and 11.4 mg Nitenpyram Flavor Tablets Following Single Oral Tablet Administration

Purpose: To demonstrate blood level bioequivalence of nitenpyram following oral administration of nitenpyram swallow tablets (market formulation) and nitenpyram flavor tablets (formulation used in the pivotal studies) at the recommended minimum dose rate of 1.0 mg/kg in cats

Type of Study: Bioequivalence – two period crossover

Animals: Twelve European shorthair cats (6 males and 6 females) approximately 2 years of age with body weights ranging between 3 and 5 kg.

Study Design: The study was conducted using a two period crossover design with a two week wash out between periods.

Table IV.8 – Bioequivalence study design

Group	Approximate Dose (mg/kg)	Period 1	Period 2
Group 1	1.0	Swallow	Flavor
Group 2	1.0	Flavor	Swallow

Route of Administration: Oral

Dosage: A single oral dose of approximately 1.0 mg/kg in each period.

Investigator: Max Maurer

Study Location: Novartis
Centre de Recherche Sante Animale SA
St. Aubin, Switzerland

Results: The mean $AUC_{(0\text{-}LOQ)}$ and C_{max} parameters calculated via non-compartmental methods and 90% confidence limits are presented in table IV.9:

Table IV.9 – Mean $AUC_{(0\text{-}LOQ)}$ and C_{max} parameters

Parameter	Swallow tablet (test product) mean value (%CV)*	Flavor tablet (reference product) mean value (%CV)	90% confidence limits**
$AUC_{(0\text{-}LOQ)}$ ($ng \bullet hr \bullet mL^{-1}$)	39061 (18%)	37708 (17%)	96-111%
C_{max} (ng/mL)	4327 (15%)	4450 (15%)	94-101%

* where %CV represents intersubject error
**expressed as a ratio of test vs. reference means

Conclusions: As defined in the 1996 CVM Bioequivalence Guidance document, the test product (swallow tablet) met the criteria for bioequivalence (the confidence interval lies within ± 20% of the mean of the reference product) in terms of the $AUC_{(0\text{-}LOQ)}$ and C_{max} parameters. Therefore, the products are considered bioequivalent.

V. SAFETY STUDIES FOR CATS

1) Acute Oral Safety Study (Tolerability) in Cats with CGA-246916 (Nitenpyram) Tablets and in Combination with Lufenuron

Purpose: To evaluate the acute safety of nitenpyram in cats upon oral dosing at ten times the use rate (10X), and when concomitantly dosed with lufenuron at labeled use level (1X). Lufenuron is a commercially available insect development inhibitor.

Investigator: Brian E. Johnson, PhD

Study Location: Liberty Research
Waverly, NY

Type of Study: Laboratory safety

Animals: Eighteen domestic shorthair cats (9 male and 9 female), 7 to 8 months of age.

Study Design: The cats were divided into 3 groups of 6. Each group had 3 males and 3 females. Table V.1 presents the groups and dosages.

Table V.1 –Treatment groups for nitenpyram cat tolerance study

Group	Treatment
1	Control (0X)
2	Nitenpyram (10X) + Lufenuron (1X)
3	Nitenpyram (10X)

Route of Administration: Oral

Dosage: Nitenpyram was administered as ten 11.4 mg tablets per animal once daily. Lufenuron was given once as per the label instructions prior to the initiation of dosing with nitenpyram.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: 14 days

Parameters Evaluated: The cats were observed each morning and evening. A clinical observation was also made one-hour post-dosing. All cats were weighed on study days –7, 0, 7, and 14. Hematology, blood chemistry and urine samples were collected on Days –7 and 14. The animals were euthanized at the conclusion of the study. Necropsy and histopathology were performed.

Results: All cats were in good general health and survived to termination of the study. No test article-related adverse effects were reported.

Conclusions: Administration of nitenpyram tablets at 10X the recommended dose for 14 days, with and without lufenuron, did not produce any adverse effects in 7-8 month old cats.

2) Six-Week Oral Safety in Kittens Beginning at Four Weeks of Age with Nitenpyram Tablets

Purpose: To determine the potential cumulative toxicity of nitenpyram tablets administered daily to kittens, beginning at four weeks of age

Investigator: Brian E. Johnson, PhD

Study Location: Liberty Research
Waverly, NY

Type of Study: Laboratory safety

Animals: Thirty-six kittens (18 male and 18 female), approximately 4 weeks old

Study Design: The kittens were kept with their dam throughout the study, but were randomly assigned to one of three treatment groups so that within each litter there could be more than one treatment group. There were 12 kittens in each treatment group. The control group included 7 males and 5 females. The 1X and 3X groups each included 6 males and 6 females.

Route of Administration: Oral

Dosage: The kittens were dosed daily for 42 days with 1 (1X) or 3 (3X) of the 11.4 mg tablets containing nitenpyram.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: Six weeks

Parameters Evaluated: The kittens were observed each morning and evening, with an additional clinical observation one hour post-dosing. Body weight was measured weekly. Ophthalmologic and physical examinations were performed at the beginning and end of the study. Hematology, blood chemistry and urine samples were collected at the end of the study only. Necropsy and histopathology were performed.

Results: All cats were in good general health and survived to termination of the study. No test article-related adverse effects were reported. The number of Heinz bodies in the red blood cells was increased in the 3X group compared to controls, however all values were within normal limits and the increases were not associated with any other abnormalities or clinical signs.

Conclusions: Administration of nitenpyram at 1X and 3X the recommended dose daily for 6 weeks did not produce any adverse effects in kittens as young as 4 weeks of age.

3) Six-Month Oral Safety in Cats with Nitenpyram Tablets

Purpose: To determine the potential cumulative toxicity and dose-response relationship of nitenpyram tablets as high as 5X administered daily in cats for six months.

Investigator: Brian E. Johnson, PhD

Study Location: Liberty Research
Waverly, NY

Type of Study: Laboratory safety

Animals: Forty-eight domestic shorthair cats (24 male and 24 female), 8 weeks old

Study Design: The cats were divided into four groups of six male and six female cats per group. The treatment groups are presented in Table V.2.

Table V.2. –Treatment groups for 6-month cat safety study

Group	Dose
1	0X
2	1X (11.4 mg)
3	3X (34.2 mg)
4	5X (57 mg)

Route of Administration: Oral

Dosage: The 1X dose was achieved by administering a single 11.4 mg nitenpyram flavored tablet to each cat daily. Cats in the 3X and 5X groups received 3 or 5 of the 11.4 mg tablets daily. Cats were dosed once a day.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: Six months

Parameters Evaluated: A physical examination was performed at the beginning and end of the study. An ophthalmologic exam was performed before treatment began. The cats were observed twice daily in the morning and evening, with an additional observation one-hour post-dosing. A clinical examination was performed weekly. Body weight and food consumption were recorded weekly. Hematology, blood chemistry and urine samples were collected at monthly intervals beginning at Week 4. Necropsy and histopathology were performed.

Results: Animals in all groups, including controls, experienced signs of upper respiratory disease (sneezing, nasal discharge and lacrimation) during the study. Two animals treated with nitenpyram were euthanized; one from the 1X group on study day 28 that had these upper respiratory signs plus dehydration and emaciation and one from the 5X group on study day 15 that had nasal discharge, drooling, "seizure-like" spasm, vocalization and an unsteady gait. These animals were presumed to have a viral infection (based on clinical signs and necropsy findings), complicated by a secondary bacterial infection. All animals in the study had been placed on prophylactic antibiotics prior to dosing for a facility outbreak of hemolytic *Streptococcus*. The number of Heinz bodies in the red blood cells was increased in the groups treated with nitenpyram compared to controls, however all values were within normal limits and the increases were not associated with any other abnormalities or clinical signs.

Conclusions: Administration of nitenpyram at 1X, 3X, and 5X the recommended dose daily for 6 months did not produce any clinically significant adverse effects and is safe for use in kittens as young as 8 weeks of age.

4) A Laboratory Reproduction Study in Cats with Nitenpyram Tablets

Purpose: To evaluate the reproductive safety of nitenpyram in male and female breeding cats at 1X and 3X the recommended use rate.

Investigator: Irma M. Grossi, PhD

Study Location: Liberty Research
Waverly, NY

Type of Study: Laboratory safety

Animals: Seventy-two adult cats (18 male and 54 female), sexually mature and proven breeders

Study Design: The cats were divided into three groups, with 6 males and 18 females in each group. The treatment groups are presented in Table V.3.

Table V.3. –Treatment groups for cat reproductive safety study

Group	Dose
1	0X
2	1X (11.4 mg)
3	3X (34.2 mg)

Route of Administration: Oral

Dosage: The 1X dose was achieved by administering a single 11.4 mg nitenpyram flavored tablet to each cat daily. Cats in the 3X group received 3 of the 11.4 mg tablets daily. The cats were dosed daily.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: Nine months

Parameters Evaluated: A complete physical examination, including blood samples for hematology and clinical pathology, was conducted prior to beginning the trial. The cats were observed daily in the morning and evening and also one-hour post-treatment. Body weights and food consumption were recorded weekly. The kittens received a detailed physical exam weekly. An ocular exam was also performed at the conclusion of the study. Necropsy was performed.

Reproductive performance was measured using indices to compare the control and treated cats for: fertility, birth viability, viability (F_1 survival) and weaning.

Results: *Adults:* All adult study animals, with the exception of one queen, survived to the termination of the study. The queen was in the 1X treatment group. A necropsy report indicates that she suffocated after aspirating a piece of processed paper kitty litter.

No clinical signs indicative of toxicity were observed. Body weights, feed consumption, reproductive indices and spermatogenic variables were unaffected by test article administration.

Axial anterior cortical cataracts were detected in 1 male in the control group and 2 of the queens in the 3X treatment group. The cataract in the control male was in the right eye. The cataracts were bilateral in the 3X queens. The ophthalmologist who examined the cats concluded that the cataracts "may represent normal biological variation, an age-related change, or could possibly be a treatment effect."

Offspring - Average number of kittens born per litter, percentage of males per litter at birth, live litter size, postnatal kitten survival, the general physical condition of the kittens, and kitten body weights were unaffected by test article administration. No ocular changes were seen.

Conclusions: Since there were no pre-treatment ocular exams, no definitive conclusion could be drawn about the origin of the cataracts. Oral administration of nitenpyram

tablets at 1 and 3X the recommended use rate did not produce any other signs of parental or neonatal toxicity.

5) Evaluation of Possible Ocular Effects after Six Months of Oral Administration of Nitenpyram Swallow Tablets to Cats

Purpose: To further evaluate the ocular safety of nitenpyram tablets.

Investigator: Edwin I. Goldenthal, PhD

Study Location: MPI Research
Mattawan, MI

Study Type: Laboratory safety

Animals: Sixteen, female, domestic shorthair cats, 7-8 month of age (only females were included because the cataracts seen at 3X in study 4 above were in female cats).

Study Design: The cats were divided into two groups of eight animals. One group was treated with a daily dose of 57 mg nitenpyram (5X the daily recommended dose). The other group was sham-dosed and served as the control.

Route of Administration: Oral

Dosage: Each cat in the treatment group was given 5 - 11.4 mg nitenpyram swallow tablets once daily.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given).

Duration of Study: Six months

Parameters Evaluated: The cats were observed twice daily throughout the study. Clinical exams were performed weekly. Body weights and food consumption were recorded weekly. Ophthalmic exams were performed pretest, at 3 months, and at 6 months. Complete physical exams were performed pre-test and at 6 months. Necropsy was performed.

Results: All cats were in good general health and survived to termination of the study. No test article-related changes were seen in the clinical signs, body weights, food consumption, physical, and macroscopic pathology. No test article-related ophthalmological findings were found.

Conclusions: Administration of 5X the recommended dose daily for six months did not produce any evidence of ocular changes.

6) Potential for Interactions Between Nitenpyram (5X) and Commercial Ectoparasiticides

Purpose: To examine the possibility of adverse interactions between nitenpyram tablets and commercially available ectoparasiticides when used concurrently in kittens.

Investigator: Irma M. Grossi, PhD

Study Location: Liberty Research
Waverly, NY

Type of Study: Laboratory safety

Animals: Twelve domestic shorthair kittens, 6 to 16 weeks of age

Study Design: The kittens were divided into 4 groups of 3. All kittens were dosed with nitenpyram once daily and treated with a commercially available product according to label instructions. Table V.4 presents the treatment groups.

Table V.4 –Treatment groups for cat drug interaction study

Active	Treatment
carbaryl powder	One application per week; kittens $\geq$ 6 weeks of age*
fipronil spray	One application; kittens $\geq$ 8 weeks of age*
imidacloprid spot-on	One application; kittens $\geq$ 16 weeks of age*
pyrethrin spray**	One application per week; kittens $\geq$ 6 weeks of age*

*All kittens concurrently received 5-11.4 mg nitenpyram tablets (5X) daily for 14 days.
**Actives: Pyrethrins + piperonyl butoxide & n-octylbicycloheptene dicarboximide.

Route of Administration: Nitenpyram was administered orally. The other products were administered topically.

Dosage: Each cat was given 5 flavor tablets containing 11.4 mg nitenpyram once daily (5X) for 14 days. Dosages for the topical products were in accordance with label directions.

Controls: None

Duration of Study: Fourteen days

Parameters Evaluated: Observations included: twice daily mortality checks, general observations noted during dosing, feeding, watering, cage cleaning activities, and weekly weight measurement.

Results: All cats were in good general health and survived to termination of the study, except for one cat in the pyrethrin group. This animal became anorexic and dehydrated during the second study week. The clinical signs and post-study macroscopic and histopathologic evaluations suggested the animal experienced "fading kitten syndrome."

Conclusions: Concomitant dosing with nitenpyram (5X the recommended dose) and one of several commercial ectoparasiticides (1X the labeled dose) did not produce treatment-related adverse effects in kittens.

VI. EFFECTIVENESS STUDIES FOR DOGS

A. DOSAGE CHARACTERIZATION

Duration of Effectiveness of Nitenpyram Used on Dogs with Fleas

Purpose: To evaluate the percent reduction in flea counts, observe the viability of fleas from dogs treated with nitenpyram and to determine the duration of effectiveness.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: K. Heeps

Study Location: Ciba-Geigy Australia Limited
Research Centre
Western Road
Kemps Creek NSW 2171

Animals: Twelve mixed breed dogs

Dosage Groups: The dogs were placed into 4 groups of 3 dogs per group. Dogs in each group were treated with 0, 0.2, 0.4 and 1.0 mg/kg on a rotating basis.

Route of Administration: Oral

Frequency of Treatment: Twice a week

Controls: Placebo

Study Design: Dogs were infested with 100 fleas 0, 1, 2, 3, 5, 7 and 16 hours post treatment on a rotating basis. Fleas were collected from the cages at 3 and 6 hours post infection. The viability of these fleas was evaluated 24 hours after collection. The study lasted 1 month.

Results: At 7 hours post treatment, the effectiveness of nitenpyram was 63.5%, 94.2% and 98.1% for the 0.2, 0.4 and 1.0 mg/kg groups, respectively. Effectiveness in the 1.0 mg/kg group stayed above 90% for the full 7 hours post treatment while it dropped below 90% in the other groups during this period. No groups showed effectiveness at 16 hours. The number of fleas that remained alive at 24 hours was lowest in the group treated with 1.0 mg/kg.

Conclusions: These data show that 1.0 mg/kg is an effective dose of nitenpyram in the dog that provides >90% effectiveness for at least 7 hours post treatment.

B. DOSAGE CONFIRMATION

1) Confirmation of an Effective Dose of Nitenpyram for the Removal of Adult Fleas on Dogs

Purpose: To confirm that the recommended use rate of nitenpyram is effective for the treatment of flea infestations on dogs.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: Suzanne Craig, DVM

Study Location: Stillmeadow, Inc.
Sugar Land, TX

Animals: Ten mixed breed and/or beagle dogs (5 males and 5 females), ≥6 months of age

Dosage Groups: Crossover design - On Day 0 each dog received placebo and on Day 7 each dog received 1-11.4 mg tablet if it weighed ≤ 25 lbs. or 1-57 mg tablet if it weighed > 25 lbs, according to the recommended dosage schedule.

Route of Administration: Oral

Frequency of Treatment: Single Dose

Controls: Placebo

Study Design: Dogs were experimentally infested with 100 cat fleas on Day -1 and Day 6. Placebo was administered on Day 0 and nitenpyram was administered on Day 7. At approximately 4 - 6 hours after treatment, each animal was combed and the cage pans examined. The number of live, dead, and moribund fleas on the animal and in the cage pan was counted and recorded. For each treatment, the total number of dead and moribund fleas on each animal was compared to the total number of fleas (including live fleas). The percentage of dead and moribund fleas was calculated.

Results: After the placebo treatment, ≤ 1.7 % of fleas on dogs were dead or moribund. After treatment with the test article, >98.2% of fleas on dogs were dead or moribund by 4-6 hours after dosing.

Conclusions: The data confirmed that nitenpyram administered orally according to the recommended dosage schedule was effective for the treatment of flea infestations on dogs.

2) The Rate of Knockdown of Fleas from Dogs Treated with Nitenpyram

Purpose: The primary objective was to demonstrate and quantify the rate of knockdown of fleas on nitenpyram treated dogs. Secondarily, the impact of flea feeding behavior on treated and untreated dogs was investigated.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: R. H. Mahoney

Study Location: Novartis Animal Health Australia Pty. Limited
R & D Centre
Yarrandoo
245 Western Road
Kemps Creek NSW 2171 Australia

Animals: Fourteen adult dogs (7 female and 7 males)

Dosage Groups: The dogs were sorted into 4 groups of 3 and 1 group of 2 based on weight and gender. The study used a 3-phase crossover design. During the 3 phases, the dogs were either treated in the morning or evening with the recommended dosage of nitenpyram or were untreated and were either infested with 100 fleas 24 hours prior to the test period or were not infested.

Route of Administration: Oral

Controls: Untreated

Duration of Study: Twelve days

Parameters Evaluated: *Time to Knockdown:* At 0.5, 1, 2, 3, and 8 hours after treatment, fleas that fell from the dogs were removed from the cages and counted. After 8 hours each dog was combed to remove any remaining live fleas.

Grooming Behavior: Scratching or grooming behavior was evaluated by videotaping the cats and comparing the activity of treated and control animals.

Results: *Time to Knockdown*: The cumulative percentage knockdown at each time period when fleas were collected is as follows:

Table VI.1 – Cumulative percentage knockdown of fleas from dogs treated with nitenpyram

Time Post-Treatment (Hours)	Cumulative % Knockdown
0.5	8.7
1.0	29.6
2.0	64.3
3.0	83.6
8.0	99.1

Grooming Behavior: Dogs showed the most grooming behavior when infested with fleas and treated with nitenpyram. Treatment without infestation did not cause irritation.

Conclusion: When dogs were given the recommended dose of nitenpyram, the product began working within 30 minutes of administration. By 8 hours post-treatment, 99.1 % of fleas had been knocked down. Nitenpyram treatment alone did not cause any behavior changes in dogs; however, flea-infested dogs showed a temporary increase in scratching and grooming behavior following treatment with nitenpyram.

3) Determination of Flea Kill Rate in Dogs Treated with Nitenpyram

Purpose: To determine the flea kill rate in dogs after oral treatment with nitenpyram.

Type of Study: Experimental infestations with cat fleas (*Ctenocephalides felis)*

Investigator: Suzanne Craig

Study Location: Stillmeadow Inc.
Sugar Land, TX

Animals: Thirty beagle and mixed breed dogs (15 males and 15 females), ≥6 months of age.

Dose Groups: The dogs were divided into three groups – control, 0.4 mg/kg and 1.0 mg/kg with six animals in the control group and twelve in each treatment group.

Route of Administration: Oral

Frequency of Treatment: Single Dose

Controls: Untreated

Study Design: Dogs were experimentally infested with 100 cat fleas on Day -1. Fleas falling off the dogs were collected in pans underneath the cages and counted at 1, 2, 3, 4, 5, 6, 7 and 8 hours after treatment. Fleas were removed from all dogs with a flea comb 24 hours after dosing.

Results: The mean number of dead fleas collected at each time period post treatment is summarized in table VI.2.

Table VI.2 – Mean number of dead fleas collected post treatment

Group	Hours After Treatment									Mean Total Dead Fleas
	1	2	3	4	5	6	7	8	24	
Control	0.2	0.5	0.2	0.2	0.7	0.5	0.2	0.5	1.0	3.8
0.4	1.2	18.2	11.3	8.6	4.4	3.0	2.9	0.6	1.3	51.5
1.0	8.8	29.2	7.9	6.5	1.6	1.8	0.8	0.6	0.7	57.9

Conclusions: By 4 hours post-treatment at the minimum recommended dose of 1.0 mg/kg, a mean of 52.4 fleas per dog had been collected out of the mean total collected by 24 hours (52.4/57.9 or 91%). This study supports the label statement that in dogs, nitenpyram achieves ≥90% effectiveness within 4 hours post-treatment.

C. CLINICAL FIELD STUDY

Controlled Clinical Study of Nitenpyram Flavored Tablets for the Removal of Fleas on Dogs

Purpose: To demonstrate the safety and efficacy of nitenpyram for treatment of fleas on dogs.

Type of Study: Multi-centered, double-blinded, placebo-controlled, clinical study

Investigator/Study Location: The study locations are listed in Table VI.3.

Table VI.3 – Sites for nitenpyram dog clinical study

Investigator Name	Institution	City	State
Dr. Mildred Bass	Village Veterinary Clinic	Farragut	TN
Dr. Gary H. Brotze	Creekview Veterinary Clinic	New Braunfels	TX
Dr. Bill Campaigne	Seguin Animal Hospital	Seguin	TX
Dr. Kathy Haigh	Haigh Veterinary Clinic	Shelton	WA
Dr. Jim Harris	Palmetto Animal Hospital	Florence	SC
Dr. Richard Johnson	Broadway Animal Hospital	El Cajon	CA
Dr. Dan McIlhany	Towne North Animal Hospital	San Antonio	TX
Dr. Gary Olson	Shelton Veterinary Clinic	Shelton	WA
Dr. Ann Parker	Hope Mills Road Animal Hospital	Fayetteville	NC
Dr. Jim Raab	Tri-County Animal Hospital	Fort Pierce	FL
Dr. Roger Sifferman	Bradford Park Veterinary Hospital	Springfield	MO

Animals: One hundred sixty client owned dogs, 2 lbs or greater in weight and 4 weeks of age and older, were enrolled in the study. The study population, distributed by age and weight, is presented in Tables VI.5 and VI.6 below.

Dosage Groups: The dogs were placed into two groups: nitenpyram and placebo. The distribution among treatment groups is provided in Table VI.4.

Table VI.4 – Study population by treatment group and visit

Treatment Group	Visit 1	Visit 2
Nitenpyram	108	79
Placebo	52	45
Total	160	124

Table VI.5 – Study population by treatment group and age

	Nitenpyram	Placebo
1-12 months	26	8
>1-5 years	34	25
>5-10 years	35	15
>10 years	13	4

Table VI.6 – Study population by treatment group and weight

	Nitenpyram	Placebo
2-10 pounds	9	6
>10-25 pounds	30	8
>25-80 pounds	65	33
>80-125 pounds	4	5

Dosage: Nitenpyram was administered orally once a day according to the recommended dosage schedule (minimum dose of 1.0 mg/kg) for a maximum of 16 daily treatments.

Controls: Placebo

Parameters Evaluated: Effectiveness was evaluated during two visits 7 to 14 days apart. The tablet was administered by the investigator at each of these visits. Dead, moribund, and live fleas were counted 4-6 hours after treatment.

Results: *Effectiveness***:** Within 6 hours of initial administration, the nitenpyram group showed an average 98.6% dead and moribund fleas, while the placebo group had 6.2% dead and moribund fleas. At the second visit the nitenpyram group had an average 99.1% dead and moribund fleas within 6 hours of administration compared to 13.1% for the placebo group.

Safety: There were a variety of adverse events reported during the trial. There was no evidence that any of the reported adverse events were drug-related.

Conclusions: The data demonstrate that nitenpyram administered orally according to the recommended dosage schedule (minimum dose of 1.0 mg/kg) is safe and effective for the treatment of flea infestations on dogs 4 weeks of age and older and 2 lbs body weight or greater.

D. BIOEQUIVALENCE STUDY

Blood Level Bioequivalence in Dogs of 57 mg Nitenpyram Swallow Tablets and 57 mg Nitenpyram Flavor Tablets Following Single Oral Tablet Administration

Purpose: To demonstrate blood level bioequivalence of nitenpyram following oral administration of nitenpyram swallow tablets (market formulation) and nitenpyram flavor tablets (formulation used in the pivotal studies) at the recommended minimum dose rate of 1.0 mg/kg in dogs

Type of Study: Bioequivalence – two period crossover

Animals: Twelve beagle dogs (6 males and 6 females) with body weights greater than 11 kg.

Study Design: The study was conducted using a two period crossover design with a two-week wash out between periods.

Table VI.7 –– Bioequivalence study design

Group	Approximate Dose (mg/kg)	Period 1	Period 2
Group 1	1.0	Swallow	Flavor
Group 2	1.0	Flavor	Swallow

Route of Administration: Oral

Dosage: A single oral dose of approximately 1.0 mg/kg in each period.

Investigator: Max Maurer

Study Location: Novartis
Centre de Recherche Sante Animale SA
St. Aubin, Switzerland

Results: The mean $AUC_{(0\text{-}LOQ)}$ and C_{max} parameters calculated via noncompartmental methods and 90% confidence limits are contained in Table VI.8:

Table VI.8 - Mean $AUC_{(0\text{-}LOQ)}$ and C_{max} parameters

Parameter	Swallow tablet (test product) mean value (%CV)*	Flavor tablet (reference product) mean value (%CV)	90% confidence limits**
$AUC_{(0\text{-}LOQ)}$ ($ng \bullet hr \bullet mL^{-1}$)	17422 (11%)	16937 (20%)	95-111%
C_{max} (ng/mL)	4787 (16%)	4216 (22%)	98-129%

*where %CV represents intersubject error
**expressed as a ratio of test vs. reference means

Conclusions: As defined in the 1996 CVM Bioequivalence Guidance document, the test product (swallow tablet) is not bioequivalent when compared to the reference product (flavor tablet). Though the test product (swallow tablet) meets the criteria for bioequivalence (the 90% confidence interval lies within ± 20% of the mean of the reference product) in terms of the $AUC_{(0\text{-}LOQ)}$ parameter, it does not in terms of the C_{max} parameter (90% CI = 98-129). However, since there is no concern about the superior bioavailability of the swallow tablet in regards to target animal safety, the swallow tablet formulation is acceptable.

VII. ANIMAL SAFETY STUDIES FOR DOGS

1) Oral Tolerability Study in Dogs with Nitenpyram Tablets and in Combination with Lufenuron

Purpose: To evaluate the acute safety of nitenpyram in dogs upon oral dosing at ten times the use rate (10X) and when concomitantly dosed with lufenuron at labeled use level (1X). Lufenuron is a commercially available insect development inhibitor.

Investigator: Edwin I. Goldenthal, PhD

Study Location: MPI Research
Mattawan, MI

Type of Study: Laboratory safety

Animals: Eighteen beagle dogs (9 male and 9 female), 7 months of age

Study Design: The dogs were divided into 3 groups of 6. Each group had 3 males and 3 females. Table VII.1 presents the groups and dosages.

Table VII.1 – Treatment groups for nitenpyram dog tolerance study

Group	Treatment
1	Control
2	Lufenuron (1X) + Nitenpyram (10X)
3	Nitenpyram (10X)

Route of Administration: Oral

Dosage: Nitenpyram was administered as either ten 11.4 mg tablets per animal once for those animals weighing ≤ 25 lbs. or ten 57 mg tablets per animal once for those animals weighing > 25 lbs. Lufenuron was given once as per the label instructions prior to the initiation of dosing with nitenpyram.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: 14 days

Parameters Evaluated: Each dog was observed at least once daily, for mortality and signs of overt toxicity, for a period of 14 days. Bodyweight, hematological, biochemical and urological evaluations were conducted prior to treatment and at the end of the 14-day period. At the end of the clinical observation period, the dogs were sacrificed and complete necropsy was performed.

Results: All dogs were in good general health and survived to study termination. No test article-related adverse effects were reported.

Conclusions: Administration of nitenpyram tablets once at 10X the recommended dose, with and without lufenuron, did not produce any adverse effects in 7 month old dogs.

2) Six-Week Oral Safety Study in Puppies Beginning at Four Weeks of Age with Nitenpyram Tablets

Purpose: To determine the potential cumulative toxicity of nitenpyram tablets administered daily to puppies beginning at four weeks of age.

Investigator: Edwin I. Goldenthal, PhD

Study Location: MPI Research
Mattawan, MI

Type of Study: Laboratory safety

Animals: Thirty-six beagle puppies (18 male and 18 female), approximately 4 weeks old

Study Design: The puppies were kept with their dam throughout the study, but were randomly assigned to one of three treatment groups so that within each litter there could be more than one treatment group. There were 12 puppies in each treatment group.

Route of Administration: Oral

Dosage: The puppies were dosed daily for 42 days with 1 (1X) or 3 (3X) of the 11.4 mg tablets containing nitenpyram.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: Six weeks

Parameters Evaluated: Each puppy was observed twice daily for mortality and signs of overt toxicity. Detailed clinical examinations were conducted once weekly throughout the study. Individual body weights were determined pretest, then weekly thereafter and prior to necropsy. Ophthalmic and physical exams were conducted pre-test and at termination of the study. Hematological, biochemical, and urological evaluations were conducted at termination of the study. A complete necropsy was performed on all puppies.

Results: All puppies survived to termination of the study, except for one in the 1X group that was euthanized *in extremis* on Day 32 due to coccidiosis. No test article related changes were reported in any of the variables monitored during the study.

Conclusions: Administration of nitenpyram at 1X and 3X the recommended dose daily for 6 weeks did not produce any adverse effects in 4 week old puppies.

3) <u>Six-Month Oral Safety Study In Dogs with Nitenpyram Tablets</u>

Purpose: To determine the potential cumulative toxicity and dose-response relationship of nitenpyram tablets as high as 5X administered daily in dogs for six months.

Investigator: Edwin I. Goldenthal, PhD

Study Location: MPI Research
Mattawan, MI

Type of Study: Laboratory safety

Animals: Forty-eight beagle dogs (24 male and 24 female), 8 weeks old

Study Design: The dogs were divided into four groups of six male and six female dogs per group. The treatment groups are presented in Table VII.2.

Table VII.2. –Treatment groups for 6-month dog safety study

Group	Dose
1	0X
2	1X
3	3X
4	5X

Route of Administration: Oral

Dosage: Dogs in the 1X treatment group received 1 tablet per day, the 3X group received 3 tablets per day and the 5X group received 5 tablets per day. For dogs ≤ 25 lbs. the tablet size used was 11.4 mg and for dogs > 25 lbs. the tablet size used was 57 mg.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: Six months

Parameters Evaluated: Each dog was observed twice daily for mortality and signs of overt toxicity. Detailed clinical examinations were conducted once weekly throughout the study. Individual body weights were determined pretest, then weekly thereafter and prior to necropsy. Complete physical and ophthalmoscopic exams were conducted prior to commencement of treatment and at 6 months of study. Hematological, biochemical, and urological evaluations were conducted pre-treatment and monthly thereafter. A complete necropsy was performed on all dogs.

Results: All dogs were in good general health and survived to termination of the study. No test article-related changes were reported in the clinical observations, body weights, feed intake, physical and ophthalmoscopic examination, clinical pathology laboratory studies, organ weights, and macroscopic and microscopic pathological examinations.

Conclusions: Administration of nitenpyram at 1X, 3X and 5X the recommended dose daily for 6 months did not produce any adverse effects in puppies as young as 8 weeks of age.

4) A Reproduction Study in Beagle Dogs with Nitenpyram Tablets

Purpose: To evaluate the reproductive safety of nitenpyram in male and female breeding dogs at 1X and 3X the recommended use rate.

Investigator: James Schardein

Study Location: WIL Research Laboratories, Inc.
Ashland, OH

Type of Study: Laboratory safety

Animals: Sixty beagle dogs (30 male and 30 female), >2 years old

Study Design: The dogs were divided into three groups of 10 males and 10 females each. The treatment groups are presented in Tablet VII.3.

Table VII.3 – Treatment groups for dog reproductive safety study

Group	Dose
1	0X
2	1X
3	3X

Route of Administration: Oral

Dosage: Dogs in the 1X treatment group received 1 tablet per day and the 3X group received 3 tablets per day. For dogs ≤ 25 lbs. the tablet size used was 11.4 mg and for dogs > 25 lbs. the tablet size used was 57 mg. The dogs were dosed daily.

Controls: Sham-dosed (touched the back of the tongue with the handle of the forceps to simulate dosing, but no tablets were given)

Duration of Study: Nine months

Parameters Evaluated: All animals were observed twice daily for mortality and general signs of toxicity. Animals were weighed and a detailed clinical observation was performed, on a weekly basis. An assessment of spermatogenesis was performed on all males during the pre-test period, just prior to breeding, and following the breeding period. The control and treatment groups were compared for gonadal function, estrous cycles, mating behavior, conception, length of gestation, parturition, lactation, the growth and development of offspring and weaning.

Results: *Adults* - All animals survived to study termination and no clinical signs indicative of toxicity were observed. Body weights, feed consumption, reproductive indices and spermatogenic variables were unaffected by test article administration.

Offspring - Average number of puppies born per litter, percentage of males per litter at birth, live litter size, postnatal puppy survival, the general physical condition of the puppies, and puppy body weights were unaffected by test article administration. Cleft palate was reported in one puppy from the 1X group and 2 puppies from the 3X group. Based on the bloodlines of the puppies and the incidence of cleft palate in the breeding colony, these malformations were not considered to be treatment related.

Conclusions: Oral administration of nitenpyram tablets at 1X and 3X the recommended use rate did not produce any signs of parental or neonatal toxicity.

5) Potential for Interactions Between Nitenpyram and Commercial Ectoparasiticides

Purpose: To examine the possibility of interactions between the nitenpyram tablet and several commercially available ectoparasiticides when used concurrently in puppies.

Investigator: Irma M. Grossi, PhD

Study Location: Liberty Research
Waverly, NY

Type of Study: Laboratory safety

Animals: Eighteen beagle puppies (11 males and 7 females), ranging in age from six to sixteen weeks

Study Design: The puppies were divided into 6 groups of 3. All puppies were dosed with nitenpyram once daily and treated with a commercially available product according to label instructions. Table VII.4 presents the treatment groups.

Table VII.4 –Treatment groups for dog drug interaction study

Active	Treatment
carbaryl powder	One application per week; puppies ≥ 6 weeks of age*
cythioate tablets	Every three days; puppies ≥ 12 weeks of age*
fipronil spray	One application; puppies ≥ 8 weeks of age*
fipronil spot-on	One application; puppies ≥ 10 weeks of age*
imidacloprid spot-on	One application; puppies ≥ 16 weeks of age*
pyrethrin spray**	One application per week; puppies ≥ 6 weeks of age*

*All puppies concurrently received five 11.5 mg nitenpyram tablets for 14 days.
** Actives: Pyrethrins, piperonyl butoxide & n-octylbicycloheptene dicarboximide

Route of Administration: Nitenpyram and cythioate were administered orally. The other products were administered topically.

Dosage: Each dog was given 5 flavor tablets containing 11.4 mg nitenpyram once daily (5X). Dosages for the other products were in accordance with label directions.

Controls: None

Duration of Study: 14 days

Parameters Evaluated: Observations included: twice daily mortality checks, observations noted during dosing, feeding, watering, cage cleaning activities, and weekly weight measurement.

Results: None of the puppies in any of the groups experienced any adverse side effects as a result of the treatments.

Conclusions: Concomitant dosing with nitenpyram (5X the recommended dose) and one of several commercial ectoparasiticides (1X labeled dose) did not produce adverse effects in puppies.

VIII. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in cats and dogs, which are non-food animals. 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."

IX. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that CAPSTAR™ (nitenpyram) Tablets, when used under the labeled conditions of use, are safe and effective.

Because adequate directions for the safe and effective lay use of CAPSTAR Tablets could be written, the product has been labeled for over-the-counter distribution.

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

Novartis Animal Health holds patent no. 5,750,548 which expires on April 29, 2016.

X. LABELING

A. Package Insert
B. Foil Package
C. Unit Dose Carton
D. Display Tray
E. Bulk Foil
F. Bulk Box

Copies of applicable labels may be obtained by writing:

Freedom of Information Office (HFI-35)
FDA
5600 Fishers Lane
Rockville, MD 20857