

Approval Date: June 11, 2003

FREEDOM OF INFORMATION SUMMARY

PROGRAM[®] (lufenuron) Flavor Tabs[®]

and

CAPSTAR[®] (nitenpyram) Tablets

FLEA MANAGEMENT SYSTEM[®]

NADA 141-205

This New Animal Drug Application is for the concurrent use of PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets in dogs and puppies to kill adult fleas and prevent flea eggs from hatching. The effects of PROGRAM[®] Flavor Tabs[®], which prevent and control flea populations, and CAPSTAR[®] Tablets, which treat flea infestations, are combined to provide a FLEA MANAGEMENT SYSTEM[™].

This New Animal Drug Application is for the concurrent use of PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets in cats and kittens to kill adult fleas and prevent flea eggs from hatching. The effects of PROGRAM[®] Flavor Tabs[®], which control flea populations, and CAPSTAR[®] Tablets, which treat flea infestations, are combined to provide a FLEA MANAGEMENT SYSTEM[™].

Novartis Animal Health US, Inc.

Greensboro, NC 27408

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1. GENERAL INFORMATION:

- a. *File Number:* NADA 141-205
(NADA 141-035 [PROGRAM[®] Flavor Tabs[®]])
(NADA 141-175 [CAPSTAR[®] Tablets])
- b. *Sponsor:* Novartis Animal Health US, Inc.
3200 Northline Avenue, Suite 300
Greensboro, NC 27408

Drug Labeler Code: 058198
- c. *Established Names:* lufenuron and nitenpyram
- d. *Proprietary Names:* PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets
FLEA MANAGEMENT SYSTEM[™]
- e. *Dosage Form:* Oral Tablets
- f. *How Supplied:* PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets are not co-packaged for this concurrent use approval. Each drug product is packaged individually as described below.

PROGRAM[®] Flavor Tabs[®] are available in four tablet sizes (see Dosage section), formulated according to the weight of the dog and cat. Each tablet size is available in color-coded packages of six tablets each.

CAPSTAR[®] Tablets are available in two tablet sizes (see Dosage section), formulated according to the weight of the dog and cat. Each tablet size is available in color-coded packages of six tablets each.
- g. *How Dispensed:* Both CAPSTAR[®] Tablets and PROGRAM[®] Flavor Tabs[®] are OTC drug products

The PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] FLEA MANAGEMENT SYSTEM[™] is OTC.
- h. *Amount of Active Ingredients:* PROGRAM[®] Flavor Tabs: 45 mg, 90 mg, 204.9 mg and 409.8 mg

CAPSTAR[®] Tablets: 11.4 mg and 57 mg
- i. *Route of Administration:* Oral
- j. *Species/Class:* Dogs and Cats

k. *Recommended Dosage:*

For Use in Dogs:

The recommended dosages are based on weight ranges and are listed below in Table 1.

Table 1: Dog Dosage

Body Weight	Dose	CAPSTAR[®] Once or twice weekly* (nitenpyram/ tablet)	PROGRAM[®] Flavor Tabs[®] Once per month (lufenuron/tablet)
2 to 10 lbs	1 tablet	11.4 mg	45.0 mg
11 to 20 lbs	1 tablet	11.4 mg	90.0 mg
21 to 25 lbs	1 tablet	11.4 mg	204.9 mg
26 to 45 lbs	1 tablet	57.0 mg	204.9 mg
46 to 90 lbs	1 tablet	57.0 mg	409.8 mg
91 to 125 lbs	1 tablet	57.0 mg	**

*If adult fleas are seen

**Dogs over 90 lbs are provided the appropriate combination of PROGRAM[®] Flavor Tabs[®].

For Use in Cats:

The recommended dosages are based on weight ranges and are listed below in Table 2.

Table 2: Cat Dosage

Body Weight	Dose	CAPSTAR[®] Once or twice weekly* (nitenpyram/tablet)	PROGRAM[®] Flavor Tabs[®] Once per month (lufenuron/tablet)
2-6 lbs	1 tablet	11.4 mg	90 mg
7-15 lbs	1 tablet	11.4 mg	204.9 mg
16-25 lbs	1 tablet	11.4 mg	**

* If adult fleas are seen

**Cats over 15 lbs are provided the appropriate combination of PROGRAM[®] Flavor Tabs[®].

l. *Pharmacological Category:*

Nitenpyram is a flea adulticide.

Lufenuron is an insect development inhibitor.

m. *Indications:*

For use in Dogs:

In dogs and puppies, the concurrent use of PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets is indicated to kill adult fleas and prevent flea eggs from hatching. The effects of PROGRAM[®] Flavor Tabs[®], which prevent and control

flea populations, and CAPSTAR[®] Tablets, which treat flea infestations, are combined to provide a FLEA MANAGEMENT SYSTEM[™].

For use in Cats:

In cats and kittens, the concurrent use of PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets is indicated to kill adult fleas and prevent flea eggs from hatching. The effects of PROGRAM[®] Flavor Tabs[®], which control flea populations, and CAPSTAR[®] Tablets, which treat flea infestations, are combined to provide a FLEA MANAGEMENT SYSTEM[™].

2. EFFECTIVENESS:

a. Dosage Characterization: Refer to the original FOI summaries for PROGRAM[®] Flavor Tabs[®] (NADA 141-035, November 23, 1994) and CAPSTAR[®] Tablets (NADA 141-175, October 20, 2000) and the supplemental FOI summary for PROGRAM[®] Flavor Tabs[®] (NADA 141-035, January 23, 1997) for this information.

b. Substantial Evidence:

(1) Laboratory Studies for Dogs

**NONINTERFERENCE AND CONFIRMATION OF EFFECTIVENESS
AGAINST ADULT FLEAS**

Title: Determination of the Efficacy of CAPSTAR[®] Used Alone and in Combination with PROGRAM[®] Flavor Tabs[®] and SENTINEL^{®1} Flavor Tabs[®] Against Fleas on Dogs in a Simulated Home Environment.

Type of Study: Laboratory effectiveness (simulated home environment)

Purpose: To evaluate nitenpyram and lufenuron adulticidal efficacy, when dosed independently and in combination, against established flea populations.

Investigator: Adelberto Perez De Leon, MVZ, MS, PhD

Study Location: Stillmeadow, Inc., Sugarland, Texas

Animals: 72 Beagle dogs (41 males and 31 females), adults, > 6 months of age, between 14.1 and 35.2 pounds.

Dosage Groups and Frequency of Treatment:

¹The results for the two Sentinel[®] treatment groups (9 dogs per group) are addressed in the FOI summary for NADA 141-204.

Table 1: Dosage groups

Dosage Group	PROGRAM [®] Flavor Tabs* [®]	CAPSTAR [®]
Untreated control	NA	NA
PROGRAM [®] Flavor Tabs [®] only (lufenuron)	0, 30, 58	NA
CAPSTAR [®] only (nitenpyram)	NA	Twice weekly
PROGRAM [®] Flavor Tabs [®] + CAPSTAR [®]	0, 30, 58	Twice weekly
CAPSTAR [®] only	NA	Once weekly
PROGRAM [®] Flavor Tabs + CAPSTAR [®]	0, 30, 58	Once weekly

*Numbers indicate study days dogs were dosed with PROGRAM[®] Flavor Tabs[®]

Route of Administration: Oral

Dosage:

Table 2: Dosage Table

Product	Weight Range (Pounds)	Lufenuron (mg/tablet)	Nitenpyram (mg/tablet)
PROGRAM [®] Flavor Tabs [®]	Up to 10	45.0	NA
	11-20	90.0	NA
	21 to 45	204.9	NA
	46 to 90	409.8	NA
CAPSTAR [®] Tablets	2 – 25	NA	11.4
	25.1-125	NA	57.0

Control: Untreated

Study Design: Seventy-two dogs were divided into eight groups of nine dogs each and housed in simulated home environments. Flea infestations were established and dogs were dosed according to Table 2. Weekly, on Days 14, 21, 28, 35, 42, 49, 56, and 63, fleas on each animal were counted.

Results: The results are presented in Table 3. CAPSTAR[®] administered two times per week, with or without PROGRAM[®] Flavor Tabs[®], was effective in reducing fleas by 90% or more by Day 14. By Day 21, CAPSTAR[®] administered one time per week, with or without PROGRAM[®] Flavor Tabs[®], was effective in reducing fleas by 90% or more. Greater than 90% control was achieved with PROGRAM[®] Flavor Tabs[®] on Days 35, 56 and 63. The results in bolded text indicate 90% or greater effectiveness.

Table 3: Effectiveness against Adult Fleas

Dosage Group	Percent Effectiveness (%)							
	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63
PROGRAM [®]	-53.9	27.3	89.4	91.6	85.2	88.7	94.1	97.5
CAPSTAR [®] TWICE WEEKLY	99.2	98.9	98.2	99.6	99.6	99.8	99.7	99.5
PROGRAM [®] + CAPSTAR [®] TWICE WEEKLY	98.0	98.7	99.1	99.8	99.8	99.7	99.9	99.7
CAPSTAR [®] ONCE WEEKLY	70.3	91.9	97.0	97.6	98.1	98.0	99.0	98.9
PROGRAM [®] + CAPSTAR [®] ONCE WEEKLY	79.1	96.2	97.2	99.0	98.4	99.7	99.4	99.4

Adverse Reactions: One dog in the CAPSTAR[®] twice weekly group developed swollen eyes and a fever of 103.5 degrees F on Day 36 (one day after CAPSTAR[®] administration). The eyes were treated with a topical steroid and antibiotic solution and the problem resolved. The relationship with drug treatment is unclear.

Conclusions: CAPSTAR[®], alone or concurrently with PROGRAM[®] Flavor Tabs[®], provided a greater reduction in adult flea counts in dogs than PROGRAM[®] Flavor Tabs[®] used alone. CAPSTAR[®] dosed twice weekly resulted in faster reduction in adult flea counts in dogs than CAPSTAR[®] dosed once weekly.

**NONINTERFERENCE OF EFFECTIVENESS AGAINST ADULT FLEAS
AND FLEA EGG HATCH**

Title: The Effectiveness of PROGRAM[®] (lufenuron) Flavor Tabs[®], SENTINEL[®] Flavor Tabs^{®2} and CAPSTAR[®] Tablets on Flea Mortality and Reproduction in Dogs.

Purpose: To assess the effectiveness of CAPSTAR[®] as an adulticide and PROGRAM[®] Flavor Tabs[®] as a flea egg inhibitor when used separately and concurrently.

Type of Study: Laboratory effectiveness (non-interference)

Investigator: Larry Cruthers, PhD

Study Location: PLRS Laboratory, Corapeake, North Carolina

Animals: 48 mixed breed dogs (24 males and 24 females), adult, > 6 months of age, between 15 and 51 pounds.

Dosage Groups: PROGRAM[®] Flavor Tabs[®] only (lufenuron), CAPSTAR[®] only (nitenpyram), PROGRAM[®] Flavor Tabs[®] + CAPSTAR[®], Untreated Control

Frequency of Treatment: PROGRAM[®] Flavor Tabs[®] were administered on Day 0 only. CAPSTAR[®] was administered on Days 0, 7, 14, 21, and 28.

Route of Administration: Oral

Dosage:

Table 4: Dosage Table

Product	Weight Range (Pounds)	Lufenuron (mg/tablet)	Milbemycin (mg/tablet)	Nitenpyram (mg/tablet)
PROGRAM [®] Flavor Tabs [®]	Up to 10	45.0	NA	NA
	11-20	90.0	NA	NA
	21 to 45	204.9	NA	NA
	46 to 90	409.8	NA	NA
CAPSTAR [®] Tablets	2 – 25	NA	NA	11.4
	25.1-125	NA	NA	57.0

²The results for the two Sentinel[®] treatment groups (8 dogs per group) are addressed in the FOI summary for NADA 141-204.

Control: Untreated

Study Design: Forty-eight adult dogs were randomly allocated to six treatment groups. Dogs were infested with fleas prior to the beginning of the study. Dogs were treated on Day 0 and then reinfested with approximately 150 fleas on Days 4, 11, 18 and 26. Three days after each infestation, flea eggs were collected from beneath the kennels. The treatment effect on flea developmental success was evaluated by incubating the collected eggs for 35 days, and determining the number of viable adult fleas produced. On Day 1 and four days after each infestation, the dogs were combed free of fleas, and the fleas were counted. Treatment effect on adult fleas was found by comparing the number of adult fleas recovered during a flea comb to the number of fleas placed on the animal.

Results: The results are presented in Table 5. Treatment groups containing PROGRAM[®] Flavor Tabs[®] had significantly reduced cumulative developmental success rates during the treatment period. Treatment groups containing CAPSTAR[®] had significantly reduced cumulative adult flea counts during the treatment period.

Table 5: Developmental and Adulticidal Effectiveness

Dosage Group	Cumulative Developmental Success (%) ¹	Cumulative Percent Effectiveness (%) ³	Cumulative Adult Flea Counts ²	Cumulative Adulticidal Effectiveness (%) ³
CAPSTAR [®]	57.4	18.9	0.0*	100.0
PROGRAM [®]	0.4*	99.4	443.3	11.8
PROGRAM [®] + CAPSTAR [®]	1.5*	97.9	1.0*	99.8
Untreated Control	70.8	--	502.5	--

* Significantly less than untreated control (p < .0001).

¹ The cumulative developmental success was calculated by summing all of the eggs that hatched from all collection days and dividing it by the total number of eggs collected.

² The cumulative adult flea counts were calculated by summing all adult fleas that were combed over all collection days.

³ The cumulative percentages were calculated by using the geometric means based on the cumulative counts.

Adverse Reactions: Two dogs in the PROGRAM[®] Flavor Tabs[®] + CAPSTAR[®] group vomited on Day 30, 24 hours after administration of both drugs. One of those dogs also vomited on Day 1, 24 hours after administration of both products. One dog in the PROGRAM[®] Flavor Tabs[®] + CAPSTAR[®] group experienced a bout of diarrhea 24 hours after administration of both products on Day 0.

Conclusions: Concurrent treatment with CAPSTAR[®] with PROGRAM[®] Flavor Tabs[®] did not interfere with the effectiveness of PROGRAM[®] Flavor Tabs[®] to inhibit the development of fleas or the effectiveness of CAPSTAR[®] to kill adult fleas. Treatment with PROGRAM[®] Flavor Tabs[®] alone is effective in preventing flea development but has a negligible effect on adult fleas in dogs. CAPSTAR[®] is

effective as a flea adulticide in dogs, although it has minimal effects on flea development.

(2) Laboratory Studies for Cats

**NONINTERFERENCE AND CONFIRMATION OF EFFECTIVENESS
AGAINST ADULT FLEAS**

Title: Determination of the Effectiveness of CAPSTAR® Used Alone and in Combination with PROGRAM® against Fleas on Cats in a Simulated Home Environment.

Purpose: To evaluate the performance of CAPSTAR® used alone or in combination with PROGRAM® Flavor Tabs® for the treatment of flea infestations on cats.

Type of Study: Laboratory effectiveness (simulated home environment)

Investigator: Adelberto A. Perez de Leon, MVZ, MS, PhD

Study Location: Stillmeadow, Inc., Sugarland, Texas

Animals: 36 mixed-breed cats (17 males and 19 females), adults, > 6 months of age, between 5.9 and 11.6 pounds.

Dosage Groups and Frequency of Treatment:

Table 6: Dosage Groups:

Dosage Group	PROGRAM ⁰ Flavor Tabs ⁰¹	CAPSTAR ⁰
Untreated control	NA	NA
PROGRAM ⁰ Flavor Tabs ⁰ only (lufenuron)	0, 30, 58	NA
CAPSTAR ⁰ only (nitenpyram)	NA	Twice weekly
PROGRAM ⁰ Flavor Tabs ⁰ + CAPSTAR ⁰	0, 30, 58	Twice weekly
CAPSTAR ⁰ only	NA	Once weekly
PROGRAM ⁰ Flavor Tabs ⁰ + CAPSTAR ⁰	0, 30, 58	Once weekly

¹Days on which cats were treated with PROGRAM⁰ Flavor Tabs⁰

Route of Administration: Oral

Dosage:

Table 7: Dosage Table

Body Weight	Dose	CAPSTAR[®] Once or twice weekly (nitenpyram/tablet)	PROGRAM[®] Flavor Tabs[®] Once per month (lufenuron/tablet)
2-6 lbs	1 tablet	11.4 mg	90 mg
7-15 lbs	1 tablet	11.4 mg	204.9 mg
16-25 lbs	1 tablet	11.4 mg	*

*Cats over 15 lbs are provided the appropriate combination of PROGRAM[®] Flavor Tabs[®].

Control: Untreated

Study design: Thirty-six cats were divided into six groups of six cats each. Simulated home environments (SHE) were created using specially designed 4 x 8 ft. cubicles with raised carpeted areas covering half the floor space. Flea infestations were established in each SHE by infesting each animal with 50 newly-emerged, unfed cat fleas on Days -25, -22, -19, -15 and -12. Approximately 21 days following the initial infestation, animals were combed, fleas were counted, and cats were reinfested. Cats were dosed two days later (Day 0). On Days 5, 13, 26, 33, 41, 48, 55, and 62, each animal was combed free of fleas. The number of live fleas was recorded for each animal and the fleas were replaced on the same animal.

Results: The results are presented in Table 8. CAPSTAR[®] only, dosed twice weekly, and CAPSTAR[®], dosed twice weekly, plus PROGRAM[®] Flavor Tabs[®] achieved 96.2% and 96.5% effectiveness by Day 26. CAPSTAR[®] only, dosed once weekly, and CAPSTAR[®], dosed once weekly, plus PROGRAM[®] Flavor Tabs[®] achieved 92.7% and 98.6% effectiveness by Day 48. The results in bolded text indicate 90% or greater effectiveness.

Table 8: Effectiveness against Adult Fleas

Dosage Group	Percent Effectiveness (%)							
	Day 5	Day 13	Day 26	Day 33	Day 41	Day 48	Day 55	Day 62
PROGRAM [®]	27.8	6.1	-27.3	-8.2	49.9	87.3	95.3	81.7
CAPSTAR [®] TWICE WEEKLY	67.2	73.4	96.2	91.2	99.0	99.6	98.8	97.5
PROGRAM [®] + CAPSTAR [®] TWICE WEEKLY	61.8	73.0	96.5	95.4	93.7	98.7	96.3	99.6
CAPSTAR [®] ONCE WEEKLY	56.0	50.8	49.7	21.6	87.5	92.7	95.7	96.2
PROGRAM [®] + CAPSTAR [®] ONCE WEEKLY	52.4	56.6	81.2	77.5	86.5	98.6	97.3	96.2

Adverse Reactions: Two cats died during the study. One cat in the PROGRAM[®] Flavor Tabs[®] only group died from anemia due to severe flea infestation. The study model induces profound, early flea infestations, which can be in excess of infestations typically present in a pet's environment. Therefore, this cat's death was not considered drug related. One cat in the CAPSTAR[®] twice weekly group died of *Pasteurella pyothorax*. The relationship between this death and drug treatment is unclear.

Transient, uncomplicated ocular discharge was noted in 12 cats receiving CAPSTAR[®] Tablets, with or without PROGRAM[®] Flavor Tabs[®]. Lethargy, dehydration and fever were noted in 1 to 2 cats from the following treatment groups as shown in table 9. The relationship of these events to drug treatment is unclear.

Table 9: Distribution of clinical signs across treatment groups.

	Number of cats	Lethargy	Dehydration	Fever
Untreated Control	1	0	0	1
PROGRAM [®]	2	2	2	1
CAPSTAR [®] ONCE WEEKLY	2	2	0	1
PROGRAM [®] + CAPSTAR [®] ONCE WEEKLY	1	1	0	1

Conclusion: CAPSTAR[®], alone or concurrently with PROGRAM[®] Flavor Tabs[®], provided a faster reduction in adult flea counts in cats than PROGRAM[®] Flavor Tabs[®] used alone. CAPSTAR[®] dosed twice weekly resulted in faster reduction in adult flea counts in cats than CAPSTAR[®] dosed once weekly.

**NONINTERFERENCE OF EFFECTIVENESS AGAINST ADULT FLEAS
AND FLEA EGG HATCH**

Title: The Effectiveness of PROGRAM[®] (lufenuron) Flavor Tabs[®] and CAPSTAR[®] (nitenpyram) Tablets on Flea Mortality and Reproduction in Cats.

Purpose: To assess the effectiveness of CAPSTAR[®] as a flea adulticide and PROGRAM[®] Flavor Tabs[®] as a flea egg inhibitor when used separately and concurrently.

Type of Study: Laboratory effectiveness (non-interference)

Investigator: Byron L. Blagburn, PhD

Study Location: Auburn University, Auburn, Alabama

Animals: 32 mixed breed cats (16 males and 16 females), adult, > 6 months of age, between 5.4 and 12.0 pounds.

Dosage Groups: PROGRAM[®] Flavor Tabs[®] only (lufenuron), CAPSTAR[®] only (nitenpyram), PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®], and Untreated control

Frequency of Treatment: PROGRAM[®] Flavor Tabs[®] were administered on Day 0. CAPSTAR[®] was administered on Days 0, 7, 14, 21, and 28.

Route of Administration: Oral

Dosage:

Table 10: Dosage Table

Body Weight	Dose	CAPSTAR[®] Once or twice weekly (nitenpyram/tablet)	PROGRAM[®] Flavor Tabs[®] Once per month (lufenuron/tablet)
2-6 lbs	1 tablet	11.4 mg	90 mg
7-15 lbs	1 tablet	11.4 mg	204.9 mg
16-25 lbs	1 tablet	11.4 mg	*

*Cats over 15 lbs are provided the appropriate combination of PROGRAM[®] Flavor Tabs[®].

Control: Untreated

Study Design: Thirty-two adult cats were randomly allocated to four groups. Cats were infested with fleas prior to the beginning of the study. Cats were treated on Day 0, then reinfested with approximately 150 fleas on Days 4, 11, 18, and 25. Three days after each infestation, flea eggs were collected from beneath the kennels. Treatment effect on flea development was evaluated by incubating collected eggs for 28 days, and determining the number of viable adult fleas produced. On Day 1 and four days after each infestation, the cats were combed free of fleas, and the fleas were counted. Treatment effect on adult fleas was found by comparing the number of adult fleas recovered during a flea comb to the number of fleas placed on the animal.

Results: The results are presented in Tables 11 and 12. Treatment groups containing PROGRAM[®] Flavor Tabs[®] had significantly reduced cumulative developmental success rates during the treatment period then untreated controls. Treatment groups containing CAPSTAR[®] had significantly reduced cumulative adult flea counts during the treatment period then untreated controls.

Table 11: Effectiveness against Egg Hatch

Dosage Group	Cumulative Developmental Success (%) ¹	Percent Effectiveness (%)
CAPSTAR [®]	81.3	2.5
PROGRAM [®]	12.7*	84.8
PROGRAM [®] + CAPSTAR [®]	5.8*	93.0
Untreated Control	83.4	--

* Significantly less than untreated controls (p < .0001)

¹ The cumulative developmental success was calculated by summing all of the eggs that hatched from all collection days and dividing it by the total number of eggs collected.

Table 12: Effectiveness against Adult Fleas

Dosage Group	Cumulative Adult Flea Counts ¹	Cumulative Adulticidal Effectiveness (%) ²
CAPSTAR [®]	1.0*	99.8
PROGRAM [®]	484.0	-1.6
PROGRAM [®] + CAPSTAR [®]	1.5*	99.7
Untreated Control	476.4	--

* Significantly less than untreated controls (p < .0001)

¹ The cumulative adult flea counts were calculated by summing all adult fleas that were combed over all collection days.

² The cumulative percentages were calculated by using the geometric means based on the cumulative counts.

Adverse Reactions: Six hours after the CAPSTAR[®] dose, one cat in the CAPSTAR[®] and PROGRAM[®] Flavor Tabs[®] group appeared sedate on initial observation. He became aroused by activity around his cage and then appeared normal.

Conclusions: Concurrent treatment with CAPSTAR[®] with PROGRAM[®] Flavor Tabs[®] did not interfere with the effectiveness of PROGRAM[®] Flavor Tabs[®] to inhibit the development of fleas or the effectiveness of CAPSTAR[®] to kill adult fleas. Treatment with PROGRAM[®] Flavor Tabs[®] alone is effective in preventing flea development but has a negligible effect on adult fleas in cats. Treatment with CAPSTAR[®] is effective as a flea adulticide in cats, but it has minimal effects on flea development.

(3) Field Study

Title: Controlled Clinical Trial of Nitenpyram Flavored Tablets for the Rapid Removal of Fleas on Dogs and Cats.

Purpose: To substantiate the effectiveness of nitenpyram for the rapid removal of fleas on dogs and cats with and without the concomitant use of PROGRAM[®] Flavor Tabs[®].

Type of Study: Three-group, multi-center, masked, placebo-controlled field study.

Investigators/Study Locations:

Mildred Bass Farragut, Tennessee	Gary Brotze New Braunfels, Texas
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Bill Campaigne Seguin, Texas	Kathy Haigh Shelton, Washington
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Jim Harris Florence, South Carolina	Richard Johnson El Cajon, California
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Dan McIlhany San Antonio, Texas	Gary Olson Shelton, Washington
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Ann Parker Fayetteville, North Carolina	Jim Raab Fort Pierce, Florida
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Roger Sifferman
Springfield, Missouri

Animals: 265 cats, 273 dogs, of various ages, weights, breeds, and sexes.

Dosage Groups and Frequency of Treatment: PROGRAM[®] Flavor Tab[®] were administered at the initial and final visits (7-14 days after initial visit). Nitenpyram tablets were administered daily for 7-14 days. Placebo tablets were administered daily and at the initial and final visits (7-14 days after initial visit).

Route of Administration: Oral

Dosage: PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] tablets were dosed according to the following table.

Table 13: Dosage Table

Product	Species	Weight Range (Pounds)	Lufenuron (mg/tablet)	Nitenpyram (mg/tablet)
PROGRAM [®] Flavor Tabs [®]	Feline	Up to 6	90	NA
		7 – 15	204.9	NA
	Canine	Up to 10	45.0	NA
		11-20	90.0	NA
		21 to 45	204.9	NA
	46 to 90	409.8	NA	
Nitenpyram Tablets	Both	2 – 25	NA	11.4
		25.1-125	NA	57.0

Control: Placebo tablets.

Study Design: Effectiveness was evaluated during two visits 7 to 14 days apart. The investigator administered the tablet to the pet at each of these visits. Live, dead, and moribund fleas were counted four to six hours after administration of the test article.

Results: The results are presented in Table 14.

Dogs: At visit 1, the nitenpyram and nitenpyram + PROGRAM[®] Flavor Tabs[®] groups showed an average of 98.6 and 98.5 percent dead and moribund fleas, respectively, within six hours of administration. In contrast, a 6.2 percent dead and moribund rate for the placebo treated group was observed. At visit 2, the two treated groups had 99.1 and 99.3 percent dead and moribund fleas within six hours of administration. Placebo treated dogs had a mean of 13.1 percent dead and moribund fleas.

Cats: At visit 1, the nitenpyram tablets and nitenpyram tablets + PROGRAM[®] Flavor Tabs[®] groups showed an average 98.4 and 98.7 percent dead or moribund fleas, respectively, within six hours of administration. In contrast, a 5.7 percent dead or moribund rate for the placebo treated groups was observed. At visit 2, the two treated groups showed efficacies of 99.9 and 99.7 percent dead and moribund fleas within six hours of administration.

Table 14: Effectiveness against Adult Fleas between Visit 1 and Visit 2

Dosage Group	Dogs		Cats	
	Visit 1 n=273	Visit 2 n=206	Visit 1 n=265	Visit 2 n=149
Control	6.2% (n=52)	13.1% (n=45)	5.7% (n=52)	3.4% (n=46)
Nitenpyram	98.6% (n=108)	99.1% (n=79)	98.4% (n=105)	99.9% (n=59)
Nitenpyram + PROGRAM [®]	98.5% (n=113)	99.3% (n=82)	98.7% (n=108)	99.7% (n=44)

Adverse Reactions: None reported.

Conclusions: Nitenpyram, alone or in combination with PROGRAM[®] Flavor Tabs[®], is safe and effective for the treatment of flea infestations in dogs and cats. At both time points, nitenpyram, alone or in combination with PROGRAM[®] Flavor Tabs[®], was more than 98% effective within 6 hours of treatment.

3. TARGET ANIMAL SAFETY: The safety of the concurrent use of PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets was established with the marketing approval of NADA 141-175 (Approval date: October 20, 2000), CAPSTAR[®] Tablets. Refer to the Freedom of Information Summary NADA 141-175 for this information.

4. HUMAN SAFETY:

This concurrent use is intended for use in dogs and cats, which are non-food animals. Because this new animal drug concurrent use is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

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.”

5. AGENCY CONCLUSIONS:

The data in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] Tablets, when used concurrently under labeled conditions, are safe and effective to kill adult fleas and prevent flea eggs from hatching.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

PROGRAM[®] is under the following U.S. patent numbers:

<u>U.S. Patent Number:</u>	<u>Date of Expiration:</u>
5,416,102	May 30, 2012
5,420,163	May 30, 2012
4,798,837	January 31, 2006
5,153,224	October 6, 2009

CAPSTAR[®] is under the following U.S. patent number:

<u>U.S. Patent Number:</u>	<u>Date of Expiration:</u>
5,750,548	April 29, 2016

6. ATTACHMENTS: Facsimile Labeling is attached as indicated below:

PROGRAM[®] Flavor Tabs[®] and CAPSTAR[®] FLEA MANAGEMENT SYSTEM[™] inserts—canine and feline.