

Approval Date: June 11, 2003

FREEDOM OF INFORMATION SUMMARY

SENTINEL[®] (milbemycin oxime/lufenuron) Flavor Tabs[®]

and

CAPSTAR[®] (nitenpyram) Tablets

FLEA MANAGEMENT SYSTEM[®]

NADA 141-204

Novartis Animal Health US, Inc.

Greensboro, NC 27408

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

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1. GENERAL INFORMATION:

- a. File Number: NADA 141-204
(NADA 141-035 [SENTINEL[®] 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: milbemycin oxime/lufenuron and nitenpyram
- d. Proprietary Names: SENTINEL[®] Flavor Tabs[®] and CAPSTAR[®]
Tablets FLEA MANAGEMENT SYSTEM[™]
- e. Dosage Form: Oral tablets
- f. How Supplied: SENTINEL[®] Flavor Tabs[®] and CAPSTAR[®]
Tablets are not co-packaged for this concurrent
use approval. Each drug product is packaged
individually as described below.

SENTINEL[®] Flavor Tabs[®] are available in
four tablet sizes (see Dosage section),
formulated according to the weight of the dog.
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. Each
tablet size is available in color-coded packages
of six tablets each.
- g. How Dispensed: Rx for the concurrent use of SENTINEL[®]
Flavor Tabs[®] and CAPSTAR[®] Tablets.
- h. Amount of Active Ingredients: Refer to Recommended Dosage Schedule
below for this information.
- i. Route of Administration: Oral
- j. Species/Class: Dogs

- k. Recommended Dosage: The recommended dosage is based on a weight range.

Recommended Dosage Schedule

Body Wt. In Pounds	Dose	CAPSTAR [®] (nitenpyram) Once or twice weekly*	SENTINEL [®] (lufenuron/milbemycin oxime) Once per month
2 to 10	1 tablet	11.4 mg	46 mg/2.3 mg
11 to 25	1 tablet	11.4 mg	115 mg/5.75 mg
26 to 50	1 tablet	57.0 mg	230 mg/11.5 mg
51 to 100	1 tablet	57.0 mg	460 mg/23.0 mg
101 to 125	1 tablet	57.0 mg	Dogs > 100 lbs are provided the appropriate combination of tablets.

*CAPSTAR[®] is administered only if adult fleas are seen.

- l. Pharmacological Category: Nitenpyram is a flea adulticide.
Lufenuron is an insect development inhibitor.
Milbemycin oxime is an anthelmintic.

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

2. EFFECTIVENESS:

The effect of SENTINEL[®] Flavor Tabs[®] on heartworm disease caused by *Dirofilaria immitis*, and the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworm) and

Trichuris vulpis (whipworm) infections is not addressed in this summary. Please see the NADA 141-084 FOI summary dated April 10, 1997, and individual product labeling for that information.

a. Dosage Characterization: Refer to the original FOI summaries for SENTINEL[®] Flavor Tabs[®] (NADA 141-084, April 10, 1997) and CAPSTAR[®] Tablets (NADA 141-175, October 20, 2000) for this information.

b. Substantial Evidence:

(1) Non-interference and Confirmation of Effectiveness against Adult Fleas

Title: Determination of the Efficacy of CAPSTAR[®] Used Alone and in Combination with PROGRAM[®] Flavor Tabs[®]¹ and SENTINEL[®] 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: Table 1 lists the dosage groups for CAPSTAR[®] and SENTINEL[®] Flavor Tabs[®] in this study.

¹ The results for the 3 Program treated groups (27 dogs) are addressed in the FOI summary for NADA 141-205.

Table 1. Dosage Groups for Non-interference and Confirmation of Effectiveness against Adult Fleas

Treatment Group	Treatment and frequency ¹	
	<u>SENTINEL[®]</u> <u>Flavor Tabs[®]</u>	<u>CAPSTAR[®]</u>
Untreated control	NA	NA
CAPSTAR [®] only	NA	Twice weekly
CAPSTAR [®] only	NA	Once weekly
SENTINEL [®] only	0, 30, 58	NA
SENTINEL [®] + CAPSTAR [®]	0, 30, 58	Once weekly

¹ Numbers refer to study days dogs were dosed with SENTINEL[®]

Route of Administration: Oral

Dosage: A single CAPSTAR[®] tablet or SENTINEL[®] Flavor Tab[®] was administered in accordance with the weight ranges listed on the product labeling.

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 the recommended dosage table. 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 2. CAPSTAR[®] Tablets administered two times per week were effective in reducing fleas by greater than 90% by Day 14 and onwards. By Day 21 and onwards, CAPSTAR[®] administered one time per week reduced fleas by greater than 90%. Greater than 90% control was achieved in SENTINEL[®] + CAPSTAR[®] group by Day 28 and onwards and in the SENTINEL[®] Flavor Tabs[®] only group at Day 35 and onwards. The results in bolded text indicate 90% or greater effectiveness.

Table 2. Effectiveness against Adult Fleas

Treatment	Percent Effectiveness							
	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63
CAPSTAR [®] Twice weekly	99.2	98.9	98.2	99.6	99.6	99.8	99.7	99.5
CAPSTAR [®] Once weekly	70.3	91.9	97.0	97.6	98.1	98.0	99.0	98.9
SENTINEL [®] + CAPSTAR [®] Once weekly	52.4	81.1	94.4	97.2	98.4	97.1	98.4	98.9
SENTINEL [®]	13.1	32.7	77.6	92.7	91.3	92.7	97.9	96.6

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[®] Tablets, when administered alone or concurrently with SENTINEL[®] Flavor Tabs[®], provided a greater reduction in adult flea counts than SENTINEL[®] Flavor Tabs[®] used alone. CAPSTAR[®] Tablets administered twice weekly resulted in faster reduction in adult flea counts than CAPSTAR[®] Tablets administered once weekly.

(2) Non-interference of Effectiveness against Adult Fleas and Flea Egg Hatch

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

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

Type of Study: Laboratory effectiveness (non-interference)

² The results for 2 Program[®] treated groups (16 dogs) are addressed in the FOI summary for NADA 141-205.

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)³, SENTINEL[®] Flavor Tabs[®] (lufenuron and milbemycin oxime) + CAPSTAR[®] (nitenpyram) CAPSTAR[®] only, Untreated Control

Frequency of Treatment: SENTINEL[®] Flavor Tabs[®] – Day 0, CAPSTAR[®] – Days 0, 7, 14, 21, and 28

Route of Administration: Oral

Dosage: A single CAPSTAR[®] tablet or SENTINEL[®] Flavor Tab[®] was administered in accordance with the weight ranges listed on the product labeling.

Control: Untreated

Study Design: Forty-eight adult dogs were randomly allocated to six treatment groups. Sixteen of the dogs were randomized to 2 treatment groups that were not part of this NADA. 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 3. When compared to the untreated control, the treatment groups containing SENTINEL[®] Flavor Tabs[®] had significantly reduced cumulative developmental success rates and the treatment groups containing CAPSTAR[®] had significantly reduced cumulative adult flea counts during the treatment period.

³ The results for the Program[®] Flavor Tabs[®] groups (16 dogs) are addressed in the FOI summary for NADA 141-205.

Table 3. Developmental and Adulticidal Effectiveness

Treatment Group	Cumulative Developmental Success (%) ^a	Cumulative Percent Effectiveness ^c	Cumulative Adult Flea Counts ^b	Cumulative Adulticidal Effectiveness (%) ^c
CAPSTAR [®]	57.4	18.9	0.0*	100.0
SENTINEL [®]	6.4*	91.0	363.0	27.8
SENTINEL [®] + CAPSTAR [®]	11.4*	83.9	0.5*	99.9
Untreated Control	70.8	--	502.5	--

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

^aThe 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.

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

^cThe cumulative percentages were calculated by using the geometric means based on the cumulative counts.

Adverse Reactions: There were no adverse reactions reported for these treatment groups.

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

(3) Hookworm Non-interference (Efficacy) Study

Title: The Efficacy of SENTINEL[®] (lufenuron and milbemycin oxime) Flavor Tabs[®] and CAPSTAR[®] (nitenpyram) Tablets for the Removal of Natural Adult *Ancylostoma caninum* infections in Dogs

Purpose: The purpose of the study was to demonstrate that CAPSTAR[®] Tablets (nitenpyram), when dosed concurrently with SENTINEL[®] Flavor Tabs[®] (milbemycin oxime and lufenuron), do not impact the efficacy of SENTINEL[®] Flavor Tabs[®] for hookworm control.

Type of Study: Laboratory efficacy study

Investigator: Dwight Bowman, PhD

Study Location: CHK R&D, Stanwood, MI

Animals: Thirty-two, adult male and female, mixed breed dogs

Dosage Groups: SENTINEL[®] Flavor Tabs[®], CAPSTAR[®], CAPSTAR[®] + SENTINEL[®] Flavor Tabs[®], and Untreated Control

Frequency of Treatment:

SENTINEL[®] Flavor Tabs[®] – once, on Day 0

CAPSTAR[®] – Days 0, 1, 2, 3, 4, 5 and 6

CAPSTAR[®] + SENTINEL[®] Flavor Tabs[®] – SENTINEL[®] Flavor Tabs[®] on Day 0 and CAPSTAR[®] on Days 0, 1, 2, 3, 4, 5 and 6

Untreated Control - none

Route of Administration: Oral

Dosage: The dosage amount was per label instructions for a given weight range.

Study Design: Thirty-two dogs with natural hookworm infections were allocated to four treatment groups, dosed, then evaluated for adult intestinal worms seven days later.

Results: Untreated dogs had a group mean of 80.4 hookworms per dog. The CAPSTAR[®] treated dogs had a group mean of 44.2 hookworms per dog. Both groups dosed with SENTINEL[®] Flavor Tabs[®] showed 100% efficacy against adult hookworms.

Adverse Reactions: None reported

Conclusions: SENTINEL[®] Flavor Tabs[®] were 100% effective at removing hookworms whether given alone or concurrently with CAPSTAR[®]. The study demonstrated that CAPSTAR[®], when dosed concurrently with SENTINEL[®], does not impact the efficacy of SENTINEL[®] Flavor Tabs[®] for hookworm control.

3. TARGET ANIMAL SAFETY:

The safety of concurrent use of CAPSTAR® Tablets and SENTINEL® Flavor Tabs® was evaluated in a 90-day study.

Title: A 90-Day Oral Safety Study in Dogs: Concomitant Administration of Nitenpyram (CAPSTAR) and a Lufenuron/Milbemycin Oxime Combination (SENTINEL Flavor Tabs).

Purpose: To assess the safety of nitenpyram (CAPSTAR®; NADA 141-175) and a lufenuron/milbemycin oxime combination (SENTINEL® Flavor Tabs®; NADA 141-084) following concomitant oral administration to dogs during a 90-day study period.

Investigator: Elizabeth L. Reagan

Study Location: Liberty Research, Inc., Waverly, New York

Type of Study: Laboratory Safety

Animals: 16 beagle dogs (8 male and 8 female), 10 to 11 weeks of age at start of dosing

Study Design: The dogs were divided into 2 groups of 8 as listed in Table 4. The dogs were randomly assigned to either a test or control group such that 4 males and 4 females were included in each group.

Table 4. Treatment Groups for milbemycin oxime/lufenuron/nitenpyram Tolerance Study

Group	Treatment
Control	Sham dosed (0X)
Test	Nitenpyram 5X daily, milbemycin oxime/lufenuron 5X every 2 weeks

Route of Administration: Oral

Dosage: Nitenpyram (CAPSTAR®) was administered as five 11.4 mg tablets per animal once daily. Milbemycin oxime/lufenuron (SENTINEL® Flavor Tabs®) were administered as either five 2.3/4.6 mg tablets or five 5.75/115 mg tablets according to body weight once every two weeks.

Controls: The control dogs were sham dosed (touched at the back of the throat in a similar manner to dosing with no tablets given).

Duration of Study: 90 days

Variables Evaluated: Complete physical and ophthalmologic examinations were conducted prior to the initial treatment and prior to necropsy and the conclusion of the study. Mortality checks were conducted twice daily, whereas body weight determinations and physical examinations were performed weekly throughout the study. Clinical observations were made one hour after dosing, and at the end of the day, during the 90-day treatment phase. In addition, on the days that SENTINEL[®] Flavor Tabs[®] were administered, clinical observations were conducted hourly for the first six hours and then 8, 10, 12, 18, and 24 hours after treatment. Food and water consumption was measured daily. Prior to the treatment period and monthly thereafter, blood samples were collected for hematology, coagulation and clinical chemistry. Urine samples were also collected at the times specified for blood collection and subjected to analysis. Necropsies were performed on all animals at the end of the study and organ weights, gross findings, and histopathological examinations were recorded for a complete set of tissues.

Results: All dogs were in good general health and survived to termination of the study. The following differences between control and treated animals were reported.

Daily Observations: Both groups had soft stool, fecal mucus, and the occasional appearance of blood in the feces and diarrhea. The treated group had a higher incidence of soft stool and fecal mucus when compared to control.

Body Weights and Weight Gains: Body weights in treated dogs were significantly lower ($p < .10$) than control dogs on Days 42, 49, 63, 77, and 84. Rate of weight gain for the treated dogs was significantly lower ($p < .10$) than for control dogs.

Hematology: No significant differences were found between treated and control dogs for the hematology variables measured.

Serum Chemistry: Creatinine values were significantly higher ($p < 0.05$) for treated dogs than for controls. Serum sodium was higher ($p < 0.01$) for treated dogs than for controls. All of these values remained within the normal range.

Urinalysis: Urine pH was significantly lower ($p < .10$) for treated dogs than for controls. Specific gravity was significantly lower ($p < .10$) in treated dogs on Day 82 than for control dogs. Microscopic exam of the formed elements did not show any treatment-related effect.

Gross Post-Mortem exam: There were pale nodules noted on the stomach of 3 treated and 2 control dogs. In 4/5 cases these corresponded with microscopic observations of lymphoid hyperplasia. There was patchy reddening of the mucosal surface of the cecum in 3 treated dogs.

Histopathology: There was lymphoid hyperplasia in the stomach of treated and control dogs. The severity was possibly greater in treated female dogs when compared to control females. Congestion of the cecal mucosa was noted in the 3 treated dogs that had reddened mucosa on the gross exam.

Conclusions: Concurrent administration of CAPSTAR[®] Tablets daily for 90 days, and SENTINEL[®] Flavor Tabs[®] biweekly for 7 treatments at 5X the recommended dosage rates was well tolerated by beagle dogs beginning at 10-11 weeks of age.

4. HUMAN SAFETY:

This concurrent use is intended for use in dogs, which are non-food animals. Because this new animal drug 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 SENTINEL[®] 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.

The concurrent use of these two drug products is restricted to use by or on the order of a licensed veterinarian because professional expertise is necessary for the diagnosis of heartworms and for the safe use of SENTINEL[®] Flavor Tabs[®].

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 approval.

CAPSTAR[®] is under the following U.S. patent number: 5,750,548
Date of Expiration: April 29, 2016

SENTINEL[®] Flavor Tabs[®] is under the following U.S. patent numbers: 5,994,395 which expires January 23, 2018 and 4,547,520 which expires June 14, 2004.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Package insert for the SENTINEL[®] Flavor Tabs[®] and CAPSTAR[®] FLEA MANAGEMENT SYSTEM[™].