FREEDOM OF INFORMATION SUMMARY

PROGRAM® (Lufenuron) Cat Flavor Tabs™
NADA 141-062

1. **General Information**

New Animal Drug Application Number:	NADA 141-062
Sponsor:	Ciba-Geigy Corporation Animal Health Division Post Office Box 18300 Greensboro, NC 27419-8300
Established Name of Drug:	lufenuron
Trade Name:	PROGRAM® Cat Flavor Tabs™
Marketing Status:	Over-The-Counter (OTC)

2. **Indications For Use**

PROGRAM Cat Flavor Tabs are indicated for use in cats and kittens, six weeks of age and older, for the control of flea populations.

3. **Dosage Form**

Oral Tablets (Flavored)

4. **Route Of Administration**

PROGRAM Cat Flavor Tabs may be administered as a treat, placed directly into the cat's mouth or broken and mixed into wet food.

Give in conjunction with a full meal. In multi-cat households, cats should be separated during treatment to achieve adequate dosing in each cat.

5. **Recommended Dosage**

PROGRAM Cat Flavor Tabs are given orally, once a month, at the recommended minimum dosage of 13.6 mg lufenuron per pound (30 mg/kg) of body weight.

Recommended Dosage Schedule

Body Weight	Lufenuron Per Tablet
Up to 10 lbs.	135 mg
11 to 20 lbs.	270 mg

Cats over 20 lbs are provided the appropriate combination of tablets.

6. **Effectiveness**

Lufenuron is an insect development inhibitor which breaks the flea life cycle at the egg stage. The adult female flea is exposed to the drug when feeding on a treated cat. The drug, which has no deleterious effect on the adult flea, acts to inhibit the development of flea eggs. The mode of action is interference with the synthesis, polymerization and deposition of chitin, the major supportive component of the flea egg case and cuticle that forms the exoskeleton of larval stages.

A. **Range-Finding Study in Cats to Determine Blood Levels of Lufenuron and Its Efficacy Against Adult Flea Emergence Using Different Dosage Forms of PROGRAM.**

Purpose: PROGRAM Cat Flavor Tabs and PROGRAM Suspension were compared for flea control and changes in lufenuron blood levels

Investigator: Mark S. Holbert. B.S.

Study Location: Stillmeadow, Inc.
Sugar Land, Texas

Type of Study: Experimental infestations of the cat flea, *Ctenocephalides felis*.

Animals: Eighteen adult domestic mixed breed cats, 9 males and 9 females, ranging in weight from 2.1 to 6.6 kg were used. The 18 animals were divided into 3 groups, 1 untreated control group of 6 animals and 2 treated groups of 6 animals each.

Dosage Forms: Group 2: Lufenuron Cat Flavor Tabs
Group 3: Lufenuron Suspension, mixed with food

Route of Administration: Oral

Dose Tested: 30 mg/kg body weight

Frequency of Treatment: Once, on Day 0

Controls: Group 1: Untreated control group

Duration of Study: Cats were experimentally infested with 100 cat fleas on study Days -1, 11, and 24. The cats in groups 2 and 3 were treated with lufenuron on day 0. Flea eggs were collected from each cat on Days 5, 17, and 30. The number of adult fleas emerging from these eggs were counted 36 days after they were collected. Blood was collected on Days 1, 2, 4, 16, and 29 for analysis of lufenuron levels.

Results: Efficacy was calculated by comparing the development of eggs collected from fleas feeding on each of the 2 lufenuron-treated groups versus control animals. The following table shows the percent efficacy for each treatment group for each day eggs were collected.

Group	Percent Efficacy Relative to Control		
	Day 5	**Day 17**	**Day 30**
2	99.4	100	99.3
3	84.7	62.2	91.1

The 90% and 95% confidence intervals were calculated on the difference between the percentage of eggs with non-emerging adults using the following pairwise comparisons:

Group I versus Group II (control vs flavor tablets),
Group I versus Group III (control vs suspension), and
Group II versus Group III (flavor tablets vs suspension).

The non-emergence rate for the treatment groups were:

Group I	Control	0.4781
Group II	Flavor Tablets	0.9978
Group III	Suspension	0.8911

The 90% and 95% confidence intervals (CI) on the difference between treatment groups were:

Comparison	**90% CI**	**95% CI**
Group I vs Group II	0.500, 0.539	0.497, 0.543
Group I vs Group III	0.390, 0.436	0.386, 0.440
Group II vs Group III	0.094, 0.119	0.092, 0.121

The confidence bounds indicate that the flavor tablets and the suspension are not equivalent, and that cats treated the flavor tablets have higher incidence of flea non-emergence than cats treated with the suspension (i.e., the flavor tablets are “super” bioequivalent). Although not equivalent, the flavor tabs were more effective than the suspension in controlling flea emergence. Because these products were not compared for a determination of bioequivalence under the provisions of the Generic Animal Drug and Patent Term Restoration Act, but for a change in formulation with a different method of oral administration of the same product, this “super” bioequivalence is acceptable.

The following table shows the mean lufenuron concentrations.

Group	Mean Lufenuron Concentration (± SD) (ppb)			
	Day 1	**Day 2**	**Day 4**	**Day 29**
2	710 ± 366	373 ± 191	289 ± 112	188 ± 75
3*	1320 ± 297	967 ± 307	634 ± 141	392 ± 121

*The data from one cat with levels below the limit of quantification (50 ppb) were excluded

As shown in the table above, the higher clinical efficacy achieved by the flavor tabs was not due to higher blood levels of lufenuron. The group dosed with the suspension had higher mean lufenuron levels at every dosing period. Therefore, there is no safety concern with the "super" bioequivalence associated with the flavor tabs compared to the suspension.

Conclusions: PROGRAM Cat Flavor Tabs were more effective than PROGRAM suspension in controlling flea emergence.

This study indicates that PROGRAM Cat Tablets are "super" equivalent to PROGRAM Suspension, therefore the efficacy data provided in support of Novartis Animal Health's PROGRAM Suspension (NADA 141-026) can be used to support this approval. Refer to the Freedom of Information Summary for NADA 141-026 for additional information on efficacy studies conducted with PROGRAM Suspension.

Adverse Reactions: One cat in group 2 showed slight ocular irritation on day 30 of the study.

B. **Flavored PROGRAM (Lufenuron) Tablets: Evaluation Palatability in Cats**

Purpose: To evaluate the palatability of PROGRAM (lufenuron) Cat Flavor Tablets when administered orally to cats either free choice or by placing the tablet into the mouth and allowing the cat to chew

Investigators/Study Locations:

Jodi Black, DVM
Best Friends Veterinary Service
1328 Highway 65
Elkert, CO 81418

Mark Silvers, DVM
Cat Clinic of Greensboro
2138-B Lawndale Drive
Greensboro, NC 27408

Type of Study: Field palatability trial

Animals: 100 client owned cats with 98 completing the study and included in the analysis of palatability. Of these 98 cats, 51 were female and 47 were male.

Dosage Form: Oral tablet (flavored)

Route of Administration: The cat owners were instructed to dose the cat just prior to feeding by offering the tablet free choice from the hand, empty food dish or from the floor. If the cat didn't consume the tablet within 3 minutes the tablet was to be placed directly into the cat's mouth.

Dose Tested: Minimum of 30 mg/kg, according to the dosing scale

Frequency of Treatment: Once

Controls: None

Duration of Study: November 21 through December 9, 1995

Results: Of the 98 cats completing the study, 54 were successfully dosed for a 55% palatability rate.

Dosed Free Choice	37/98	38 %
Dosed in Mouth	17/98	17%
Total Dosed	54/98	55%

Conclusions: PROGRAM Cat Flavor Tablets are moderately palatable to cats, with a 55% acceptance rate.

Adverse Reactions: One cat developed lethargy and decreased appetite 1 day post treatment. On Day 3 post treatment, the cat's temperature was elevated at 105.0^{o}F. The cat responded to treatment with antibiotics.

C. **Flavored PROGRAM (Lufenuron) Tablets: Evaluation Dosage Form Acceptability in Cats**

Purpose: To evaluate the dosage form acceptability of PROGRAM (lufenuron) Cat Flavor Tablets when administered orally to cats either free choice, manually, or broken and mixed with wet food.

Investigators/Study Locations:

Jodi Black, DVM
Best Friends Veterinary Service
1328 Highway 65
Elkert, CO 81418

Mark Silvers, DVM
Cat Clinic of Greensboro
2138-B Lawndale Drive
Greensboro, NC 27408

Type of Study: Field dosage form acceptability trial

Animals: 100 client owned cats with 91 completing the study and included in the analysis of acceptability. Of these 91 cats, 51 were male and 40 were female.

Dosage Form: Oral tablet (flavored)

Route of Administration: The cat owners were instructed to dose the cat just prior to feeding by offering the tablet free choice from the hand, empty food dish or from the floor. If the cat didn't consume the tablet within 3 minutes the tablet was to be placed directly into the cat's mouth. If dosing was still unsuccessful, the tablet was to be broken into a small portion of wet food.

Dose Tested: Minimum of 30 mg/kg, according to the dosing scale

Frequency of Treatment: Once

Controls: None

Duration of Study: January 18 through February 12, 1996

Results: Of the 91 cats completing the study, 82 were successfully dosed for a 90% acceptability rate.

Dosed Free Choice	29/91	32%
Dosed in Mouth	34/91	37%
Dosed in Food	19/91	21%
Total Dosed	82/91	90%

Conclusions: PROGRAM Cat Flavor Tablets are an acceptable dosage form for administration to cats, with a 90% acceptance rate.

Adverse Reactions: One cat vomited once 1 day post treatment and again 11 days post treatment.

7. **Target Animal Safety**

Study A cited above indicates that PROGRAM Cat Flavor Tablets are "super" bioequivalent to PROGRAM Suspension. The superior efficacy of the flavor tablets were not due to increased blood levels of the drug, therefore the safety data provided in support of Novartis Animal Health's PROGRAM Suspension (NADA 141-026) can be used to support this approval. Refer to the Freedom of Information Summary for NADA 141-026 for additional information on target animal safety studies conducted with PROGRAM Suspension.

8. **Human Safety**

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

9. **Agency Conclusions**

The data in support of this new animal drug application comply with the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 514 of the implementing regulations. The data demonstrate that PROGRAM Cat Flavor Tabs (lufenuron), when used under labeled conditions of use, are safe and effective.

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

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

10. **Labeling (Attached)**

A. Insert

B. Blister Cards (6 Tablets)
   135 mg
   270 mg

C. Bulk Package (60 Tablets)
   135 mg
   270 mg

D. Dispensing Envelope