FREEDOM OF INFORMATION SUMMARY

PROGRAM® (Lufenuron) Cat Tablets
Supplement to NADA 141-035, For use in cats and kittens six weeksof age or older, for the control of flea populations

I. General Information

A. New Animal Drug Application Number:

Supplement to NADA 141-035

B. Sponsor:

Novartis Animal Health US, Inc.
Post Office Box 18300
Greensboro, NC 27419-8300

C. Accepted Name of Drug:

lufenuron

D. Trade Name:

PROGRAM® Cat Tabs

E. Marketing Status:

OTC

F. Effect of Supplement

Approval of the supplemental NADA will change NADA 141-035 by adding the indication for the use of lufenuron tablets in cats and kittens, six weeks of age or older, at a minimum dose of 30 mg/kg for the control of flea populations. The cat will have labeling separate from the original dog approval.

G. Indications For Use

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

H. Dosage Form

Oral Tablets

I. Route Of Administration

PROGRAM Cat Tablets should be given by direct oral dosing or broken into wet food. In either case, give in conjunction with a full meal.

The tablet may need to be broken prior to direct oral dosing for ease of administration to small cats and kittens. In multi-cat households, cats should be separated during treatment to achieve adequate dosing in each cat.

J. Recommended Dosage

PROGRAM Cat Tablets 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	Dose & Tablet Color	Lufenuron Per Tablet
Up to 6 lbs	One red tablet	90.0 mg
7 to 15 lbs	One yellow tablet	204.9 mg

Cats over 15 lbs are provided the appropriate combination of tablets.

II. 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.

1. Purpose:

   PROGRAM Tablets and PROGRAM Suspension were compared for flea control and changes in lufenuron blood levels

2. Investigator: Mark S. Holbert. B.S.

3. Study Location: Stillmeadow, Inc., Sugar Land, Texas

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

5. Animals: Twenty-two adult domestic mixed breed cats, 11 males and 11 females, ranging in weight from 2.0 to 3.2 kg were used. The 22 animals were divided into 4 groups, 1 untreated control group of 4 animals and 3 treated groups of 6 animals.

6. Dosage Forms:

   Group 2: Lufenuron Tablets, crushed and mixed with food
   Group 3: Lufenuron Tablets, pilled with tablet pieces followed immediately by food
   Group 4: Lufenuron Suspension, mixed with food

7. Route of Administration: Oral

8. Dose Tested: 30 mg/kg body weight

9. Frequency of Treatment: Two treatments, Day 0 and Day 30

10. Controls: Group 1: Untreated control group

11. Duration of Study: Cats were experimentally infested with 100 cat fleas on study Days -1, 24, 29, and 54. The cats in Groups 2 through 4 were treated with lufenuron on Days 0 and 30. Flea eggs were collected from each cat on Days 5, 30, 35, and 60. The number of adult fleas emerging from these eggs were counted 36 days after they were collected. Blood was collected at 8, 24, 48, 96 hours and 7, 21, and 29 days after treatment. The 24-, 48-, 96-hour and Day 29 blood samples were analyzed for lufenuron.

12. Results: Efficacy was calculated by comparing the development of eggs collected from fleas feeding on each of the 3 lufenuron-treated groups versus control animals. The following table shows the percent efficacy for each treatment group for each day eggs were collected.

	Percent Efficacy Compared to Control			
Group	**Day 5**	**Day 30**	**Day 35**	**Day 60**
1	N/A	N/A	N/A	N/A
2	97.0	96.4	97.7	95.5
3	90.7	88.0	98.7	92.6
4	86.8	94.1	97.6	88.2

The 95% confidence interval method was used to determine if the two forms of PROGRAM Tablets (crushed in food or manually dosed as pieces) were therapeutically equivalent to PROGRAM Suspension. The 95% confidence interval was calculated on the difference between the percent of eggs with non-emerging adults using the following pairwise treatment group comparisons:

1) Group 2 versus Group 4,
2) Group 3 versus Group 4
3) Group 1 versus Group 2
4) Group 1 versus Group 3 and
5) Group 1 versus Group 4

Each treated group had a non-emergence rate statistically significantly different from and better than the control group (comparisons 3, 4 and 5 above). Comparison 2 above (between groups 3 and 4) had a 95% confidence interval on the difference of (-0.00544, 0.01764) and Comparison 1 above (between groups 2 and 4) had a 95% confidence interval on the difference of (0.01056, 0.03104).

The following table shows the mean lufenuron concentrations.

Group	Mean Blood Concentration (± Standard Deviation)			
	Day 1	Day 2	Day 4	Day 29
2	542 ± 372	294 ± 264	299 ± 283	165 ± 172
3	344 ± 240	210 ± 152	171 ± 136	96 ± 59
4	435 ± 267	325 ± 285	192 ± 63	135 ± 59

The area under the curve (AUC) calculations to Day 29 show that the crushed tablets (Group 2) and the suspension mixed with food (Group 4) have similar bioavailabilities which are both greater than the manually dosed tablets (Group 3). However, due to the small number of animals studied and the large degree of intersubject variability, the test for treatment effects lacks the necessary power to derive meaningful statistical conclusions. Based on the efficacy parameter (egg hatch), there is no clinical difference between treatment Groups 2, 3 and 4.

13. Conclusions: PROGRAM Tablets, when administered to cats by either direct oral dosing of tablet pieces or crushed in wet food are therapeutically equivalent to PROGRAM Suspension administered in food.

    This study indicates that PROGRAM Cat Tablets are therapeutically equivalent to PROGRAM Suspension, therefore the efficacy data provided in support of PROGRAM Suspension can be referenced from NADA 141-026. Refer to the original Freedom of Information Summary for NADA 141-026 for additional information on efficacy studies conducted with PROGRAM Suspension.

14. Adverse Reactions: None reported.

B. PROGRAM (Lufenuron) Swallow Tablets: Evaluation of Dosage Form Acceptability in Cats Study # CAH-6258-95-0297

1. Purpose: To evaluate the acceptability of PROGRAM (lufenuron) Tablets when administered orally to cats

2. 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

3. Type of Study:Field dosage form acceptability trial

4. Animals: 101 client owned cats with 99 completing the study and included in the analysis of dosage form acceptability. Of these 99 cats, 42 were female and 57 were male. These cats ranged in age from 8 weeks to 12 years and in weight from 1.25 to 16.8 pounds.

5. Dosage Form: Oral tablet

6. Route of Administration: The cat owners were instructed to dose the cat just prior to feeding by first placing the tablet directly in the mouth. If dosing by this method was unsuccessful, the tablet was to be broken into a small portion of wet food and offered to the cat.

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

8. Frequency of Treatment: Once

9. Controls: None

10. Duration of Study: September 26 through October 10, 1995

11. Results: Of the 99 cats completing the study, 93 were successfully dosed for a 94% acceptance rate. Of the 93 cats accepting the tablet, 66 accepted the tablet when placed directly in the mouth and 27 accepted the tablet when broken into food.

    Manually Dosed: 66/99 (67%)
    Dosed in Food: 27/99 (27%)
    Total Dosed: 93/99 (94%)

    Some owners reported on the case report forms that the size of the pill made dosing difficult, prevented manual administration of the pill, or simply looked large compared to the size of the cat.

12. Conclusions: PROGRAM Tablets are an acceptable dosage form for administration to cats.

13. Adverse Reactions: None reported.

III. Target Animal Safety

Study A cited above indicates that PROGRAM Cat Tablets are therapeutically equivalent to PROGRAM Suspension, therefore the safety data provided in support of PROGRAM Suspension can be referenced from NADA 141-026. Refer to the original Freedom of Information Summary for NADA 141-026 for additional information on target animal safety studies conducted with PROGRAM Suspension.

IV. Human Safety

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

V. Agency Conclusions

The data in support of this supplement comply with the requirements of Section 512 of the Act and Part 514 of the implementing regulations. The data demonstrate that PROGRAM Cat Tablets (lufenuron), when used under labeled conditions of use, are safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106) this is a Category II change. This supplement provides for an additional species (cat) at a minimum dose of 30 mg/kg for the control of flea populations. The approval of this change has no adverse effect on the safety and effectiveness of the this new animal drug application. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

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

Under section 512(c)(2)(F)(iii) 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 supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new species for which the supplemental application was approved.

VI. Labeling (Attached)

1. Insert
2. Blister Cards (6 Tablets)
    a. 90 mg
    b. 204.9 mg
3. Bulk Package (60 Tablets)
    a. 90 mg
    b. 204.9 mg
4. Dispensing Envelope
    a. Outer flap
    b. Inner flap
    c. Front
    d. Back