## I. GENERAL INFORMATION

### A. File Number

NADA 141-026

### B. Sponsor

Ciba Animal Health
Ciba-Geigy Corporation
Post Office Box 18300
Greensboro, NC 27419-8300

### C. Proprietary Name

lufenuron suspension

### D. Established Name

Program® Suspension

### E. Dosage Form

Oral Suspension

### F. Dispensing Status

Rx: For use by or on the order of a licensed veterinarian

### G. Dosage Regimen

The ingredients of PROGRAM Suspension are formulated into an oral suspension, packaged in two sizes of unit dose packs, for administration as appropriate for the weight of the cat (see below) at monthly dosing intervals. Each PROGRAM Suspension unit dose pack provides the minimum recommended dose of 30 mg lufenuron per kilogram of body weight.

| Cat Weight | Unit Dose Packs Per Month | Lufenuron Per Unit Pack Dose | Unit Dose Pack Color |
|---|---|---|---|
| Up to 10 lbs. | 1 small | 135 mg | Orange |
| 11 to 20 lbs. | 1 large | 270 mg | Green |

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

### H. Route of Administration

Suspension should be mixed with food and offered to the cat. The cat should be observed to ensure that the entire dose is consumed. Give in conjunction with a full meal. In multi-cat households, cats should be separated during treatment to achieve adequate dosing in each cat.

### I. Species/Class

Cats, six weeks of age and older

### J. Indication

Suspension is indicated for use in cats, six weeks of age and older, for the control of flea populations.

## II. EFFECTIVENESS

The new animal drug application for lufenuron suspension contains adequate and well-controlled studies which demonstrate efficacy in controlling flea populations. 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. DOSE ESTABLISHMENT

Two pivotal studies, one dose titration and one dose confirmation, were conducted to establish and confirm the optimal effective dose of lufenuron for the control of flea populations caused by the cat flea, *Ctenocephalides felis*. These studies titrated and confirmed a minimum recommended monthly dose of 30 mg/kg body weight for cats. Additionally, six corroborative studies, three dose titrations and three dose confirmations, were conducted which support the efficacy of lufenuron suspension in cats. These six studies were deemed corroborative rather than pivotal either because the final market formulation or the recommended dosage was not used.

Results from these studies were derived using the following calculations:

$$\%Developmental\ Success = \frac{No.\ Adults\ Emerged}{No.\ \ Eggs\ Collected} \times 100$$

$$Mean\ \%\ Control = \frac{Mean\ \%\ Dev.\ \ Success\ (Control) - \%\ Dev.Success\ (Treated)}{Mean\ \%\ Dev.Success\ (Control)} \times 100$$

*PIVOTAL DOSE TITRATION STUDY*

*Determination of the Optimal Effective Oral Dose of Lufenuron for the Control of Reproduction in the Cat Flea,* C. felis, In Cats

**Purpose:** Dose Titration

**Investigator:** Byron L. Blagburn, PhD

**Study Location:**

Auburn University
Auburn, AL

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

**Animals:** Thirty-two domestic shorthair cats, 16 males and 16 females, ranging in age from 4.5 to 16 months and ranging in weight from 1.98 to 3.24 kg were used. The 32 animals were divided into 4 groups of 8 cats each (4 males and 4 females).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral (in food)

**Doses Tested:** 15 mg, 30 mg and 45 mg/kg body weight

**Frequency of Treatment**: One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, -3, 1, 7, 15, 23, and 29. The cats were treated on day 0. Flea eggs were collected from each cat on days -1, 0, 4, 11, 14, 18, 21, 25, 28, and 32. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The following table shows the cumulative developmental success of the eggs collected from all treatment groups to day 28 and to day 32. Since the drug is administered monthly, the critical parameter was determined to be efficacy at the end of the test period. Therefore, efficacy was evaluated through day 28 and then through day 32 to determine if there was any decrease in efficacy late in the month.

Cumulative Developmental Success Rates From Day 4 to Day 28 or From Day 4 to Day 32.

| **Treatment** | **Day 28** | **Day 32** |
|---|---|---|
| Control | 61.04% | 62.39% |
| 15 mg/kg | 1.27% | 1.52% |
| 30 mg/kg | 0.29% | 0.41% |
| 45 mg/kg | 0.23% | 0.24% |

The cumulative numbers of F1 progeny produced on days 28 or 32 were analyzed using logistic regression techniques (SAS®).

**The following table presents the results from the Wald Chi-square test using the maximum likelihood estimates:**

| | Day 28 | | Day 32 | |
|---|---|---|---|---|
| Treatment Groups | X2 | p-value | X2 | p-value |
| All Doses | 1886 | <0.0001 | 2346 | <0.0001 |
| 15,30 and 45 | 37.4 | <0.0001 | 52 | <0.0001 |
| 30 and 45 | 0.36 | 0.5489 | 2.27 | 0.1320 |

The results from the analysis of cumulative numbers of F1 progeny produced indicate the response plateaus at 30 mg/kg.

**Conclusions**: Lufenuron, administered in food at 30 mg/kg body weight, was effective (> 90%) in preventing flea egg development for 28 and 32 days-post treatment and statistical analysis indicates that the response to lufenuron plateaus at this dose.

**Adverse Reactions**: None reported. The following observations were made during the study, but were considered unrelated to treatment with lufenuron or placebo: diarrhea on study days 5 and 19 in 1 cat from the placebo group and 1 cat treated with 30 mg/kg lufenuron; vomitus found in the cage of 1 cat from the 45 mg/kg group and 1 cat from the 30 mg/kg group on study day 13; and hair loss on the nose of 1 cat in the 45 mg/kg group.

*PIVOTAL DOSE CONFIRMATION STUDY*

*Confirmation of the Optimal Effective Oral Dose of Lufenuron for the Control of Reproduction of the Cat Flea,* C. felis, in Cats.

**Purpose:** Dose Confirmation

**Investigator:** Larry R. Cruthers, Ph.D.

**Study Location:**

Professional Laboratory and Research Services, Inc.
Corapeake, NC

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

**Animals:** Twenty mixed breed adult cats (10 male and 10 female) ranging in weight from 1.45 to 3.18 kg were used in this study. The 20 cats were ranked by weight and sex, and assigned to 2 groups of 10 animals each (5 males and 5 females).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral (in food)

**Doses Tested:** Minimum recommended dose of 30 mg/kg body weight

**Frequency of Treatment**: One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -10, 0, 7, 14, 21, and 28. The cats were treated on day 0. Flea eggs were collected from each cat on days -6, -4, 4, 7, 11, 14, 18, 21, 25, 28, and 32. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The cumulative developmental success and percent control at day 32 were:

| | Results After 32 Days | |
|---|---|---|
| Treatment Group | % Developmental Success | % Control |
| Lufenuron 30 mg/kg | 2.1 | 96.5 |
| Placebo Control | 59.2 | |

**Conclusions**: Lufenuron, administered at a minimum of 30 mg/kg body weight, was effective (>90%) in preventing flea egg development for 32 days after treatment.

**Adverse Reactions**: None reported

*CORROBORATIVE DOSE TITRATION STUDIES*

*Study 1*: *Determination of the Optimal Effective Oral Dose of Lufenuron for the Control of the Cat Flea,* Ctenocephalides felis, in Cats

**Purpose:** Dose Titration

**Investigator:** Byron L. Blagburn, PhD

**Study Location:**

Auburn University
Auburn, AL

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

**Animals:** Thirty-two mixed breed cats (16 males and 16 females) approximately 6 months to one year in age and ranging in weight from 1.70 to 2.95 kg were used in this study. The 32 animals were divided into 4 groups of 8 animals each (4 females and 4 males).

**Dosage Form:** Lufenuron 15% Suspension (market formulation is 7%)

**Route of Administration:** Oral

**Doses Tested:** 7.5 mg, 15 mg and 30 mg per kg body weight

**Frequency of Treatment**: One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, 0, 14, 21, 28, 35, 42, 49, and 56. The cats were treated on day 0. Flea eggs were collected from each cat twice weekly from day -3 to day 63. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The data provided below represent the mean percent control for days 28 and 32 post-treatment. Since the drug is administered monthly, the critical parameter was determined to be efficacy at the end of a one month period. Because days 28 and 32 represent the final two egg collections of the month, the mean percent control from these two days was used to determine efficacy.

| Treatment Group<br>mg/kg | Mean % Control<br>Days 28 and 32 |
|---|---|
| 7.5 | 49.1 |
| 15.0 | 75.0 |
| 30.0 | 98.1 |

**Conclusions:** The dose of 30 mg lufenuron per kg body weight was effective (>90%) in preventing flea egg development during the critical test period (days 28 and 32). The other doses tested in this study, 7.5 mg/kg and 15 mg/kg, failed to prevent >90% flea egg development. Since the final market formulation was not used, this study is considered corroborative.

**Adverse Reactions**: None reported

*Study 2*: *Determination of the Optimal Effective Oral Dose of Lufenuron for the Control of the Cat Flea,* Ctenocephalides felis, In Cats.

**Purpose:** Dose Titration

**Investigator:** Byron L. Blagburn, PhD

**Study Location:**

Auburn University
Auburn, AL

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

**Animals:** 32 mixed breed cats (16 male and 16 female) approximately 6 months to 1 year in age and ranging in weight from 2.5 to 5.5 kg were used in this study. The 32 animals were divided into 4 groups of 8 animals each (4 male and 4 female).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral

**Doses Tested:** 10 mg, 20 mg and 40 mg/kg body weight

**Frequency of Treatment**: One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, 3, 10, 17, 21, 28, 35, 52, and 59. The cats were treated on day 0. Flea eggs were collected from each cat on days -3, -1, weekly to day 21, then twice weekly to day 63. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The data provided below represent the mean percent control for days 28 and 32 post-treatment. Since the drug is administered monthly, the critical parameter was determined to be efficacy at the end of a one month period. Because days 28 and 32 represent the final two egg collections of the month, the mean percent control from these two days was used to determine efficacy.

| Treatment Group<br>mg/kg | Mean % Control<br>Days 28 and 32 |
|---|---|
| 10 | 48.3 |
| 20 | 79.0 |
| 40 | 93.7 |

**Conclusions**: The dose of 40 mg lufenuron per kg body weight was effective (>90%) in preventing flea egg development during the critical test period (days 28 and 32). The other doses used in this study, 10 mg/kg and 20 mg/kg, failed to prevent >90% flea egg development. This study is considered corroborative since the recommended minimum effective dose of 30 mg/kg was not included.

**Adverse Reactions:** None reported.

*Study* 3: *Determination of the Optimal, Effective, Oral Dose of Lufenuron for the Control of the Cat Flea,* C. felis, in Cats.

**Purpose:** Dose Titration

**Investigator:** Byron L. Blagburn, PhD

**Study Location**:

Auburn University
Auburn AL

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

**Animals:** 32 adult mixed breed cats (15 females and 17 males), weighing between 2.20 and 5.04 kg, were used in this study. The 32 animals were divided into 4 groups of 8 animals each (3 groups of 4 males and 4 females and 1 group of 5 males and 3 females).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral

**Doses Tested:** 10 mg, 20 mg and 40 mg/kg body weight

**Frequency of Treatment**: One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, 3, 10, 17, 21, 28, 35, 52, and 59. The cats were treated on day 0. Flea eggs were collected from each cat on days -3, -1, weekly to day 21, then twice weekly to day 63. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The data provided below represent the mean percent control for days 28 and 32 post-treatment. Since the drug is administered monthly, the critical parameter was determined to be efficacy at the end of a one month period. Because days 28 and 32 represent the final two egg collections of the month, the mean percent control from these two days was used to determine efficacy. One cat in the high dose group was dosed incorrectly and was not included in the data analysis.

| Treatment Group<br>mg/kg | Mean % Control<br>Days 28 and 32 |
|---|---|
| 10 | 60.5 |
| 20 | 80.0 |
| 40 | 98.9 |

**Conclusions**: The dose of 40 mg lufenuron per kg body weight was effective (>90%) in preventing flea egg development during the critical test period (days 28 and 32). The other doses used in this study, 10 mg/kg and 20 mg/kg, failed to prevent >90%

flea egg development. This study is considered corroborative since the recommended minimum effective dose of 30 mg/kg was not included.

**Adverse Reactions:** None reported

*CORROBORATIVE DOSE CONFIRMATION STUDIES*

*Study 1*: *Confirmation of the Optimal Effective Oral Dose of Lufenuron for the Control of Reproduction in the Cat Flea,* Ctenocephalides felis, in Cats

**Purpose:** Dose Confirmation

**Investigator:** Larry R. Cruthers, PhD

**Study Location:**

Professional Laboratory and Research Services, Inc.
Corapeake, NC

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

**Animals:** Twenty adult mixed breed cats (10 males and 10 females) ranging in weight from 2.2 to 3.9 kg were used in this study. The 20 animals were divided into two groups of 10 animals each (5 males and 5 females).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral (in food)

**Dose Tested:** Minimum dose of 20 mg/kg body weight* (the actual doses administered ranged from 21 to 38.5 mg/kg with an average dose rate of 32.2 mg/kg). *This dose was initially tested as a minimum effective dose but was found to be inferior to the recommended minimum dose of 30 mg/kg, refer to the corroborative dose titration studies #2 and #3, pages 7-9).

**Frequency of Treatment:** One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, 0, 7, 14, 21, and 28. The cats were treated on day 0. Flea eggs were collected from each cat on days -3, -1, 4, 7, 11, 14, 18, 21, 25, 28, and 32. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The data provided below represent the mean percent control for days 28 and 32 post-treatment. Since the

drug is administered monthly, the critical parameter was determined to be efficacy at the end of a one month period. Because days 28 and 32 represent the final two egg collections of the month, the mean percent control from these two days was used to determine efficacy.

| Treatment Group<br>mg/kg | Mean % Control<br>Days 28 and 32 |
|---|---|
| Minimum of 20<br>(avg. 32.2) | 100 |

**Conclusions:** Lufenuron, administered at a minimum of 20 mg/kg body weight, was effective (>90%) in preventing flea egg development as measured at the end of a one month period (days 28 and 32). However, based on the data generated in corroborative dose titration studies #2 and #3, this dose was found to be inferior to the minimum effective dose of 30 mg/kg.

**Adverse Reactions:** None reported. One cat died on day 28 of the study. The results of a necropsy suggest urinary blockage and right ventricle hypertrophy as the possible cause of death.

*Study 2: Confirmation of the Optimal Effective Oral Dose of Lufenuron for the Control of Reproduction in the Cat Flea,* Ctenocephalides felis, in Cats.

**Purpose:** Dose Confirmation

**Investigator:** Larry R. Cruthers, PhD

**Study Location:**

Professional Laboratory and Research Services, Inc.
Corapeake, NC

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

**Animals:** Twenty mixed breed adult cats (4 males and 16 females) ranging in weight from 1.4 to 3.0 kg were used in this study. The 20 animals were divided into 2 groups of 10 animals each (2 males and 8 females).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral (in food)

**Doses Tested** Minimum dose of 20 mg/kg body weight (the actual doses administered ranged from 21.6 to 37.9 mg/kg with an average dose of 29.4 mg/kg)

**Frequency of Treatment:** One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, 0, 7, 14, 21, and 28. The cats were treated on day 0. Flea eggs were collected from each cat on days -3, -1, 4, 7, 11, 14, 18, 21, 25, 28, and 32. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The data provided below represent the mean percent control for days 28 and 32 post-treatment. Since the drug is administered monthly, the critical parameter was determined to be efficacy at the end of a one month period. Because days 28 and 32 represent the final two egg collections of the month, the mean percent control from these two days was used to determine efficacy.

| Treatment Group<br>mg/kg | Mean % Control<br>Days 28 and 32 |
|---|---|
| Minimum of 20<br>(avg. 29.4) | 100 |

**Conclusions:** Lufenuron, administered at a minimum of 20 mg/kg body weight, was effective (>90%) in preventing flea egg development as measured at the end of a one month period (days 28 and 32). However, based on the data generated in corroborative dose titration studies #2 and #3, this dose was found to be inferior to the minimum effective dose of 30 mg/kg.

**Adverse Reactions**: None reported

*Study 3*: *Confirmation of the Optimal Effective Oral Dose of Lufenuron for the Control of Reproduction in the Cat Flea,* Ctenocephalides felis, In Cats

**Purpose:** Dose Confirmation

**Investigator:** Robert Young, MS., D.V.M.

**Study Location:**

Young Veterinary Research
Modesto, CA

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

**Animals:** Twenty adult mixed breed cats (10 males and 10 females) over 12 months of age and ranging in weight from 2.6 to 6.2 kg were used in this study. The 20 animals were divided into 2 groups of 10 animals each (5 males and 5 females).

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral (in food)

**Doses Tested:** Minimum of 20 mg/kg body weight (the actual dose administered ranged from 22.35 to 36.84 mg/kg with an average dose of 28.7 mg/kg)

**Frequency of Treatment:** One treatment

**Controls:** Placebo oral suspension containing formulation excipients without active ingredient.

**Duration of Study:** Cats were experimentally infested with newly emerged cat fleas on study days -7, 0, 7, 14, 21, and 28. The cats were treated on day 0. Flea eggs were collected from each cat on days -3, -1, 4, 7, 11, 14, 18, 21, 25, 28, and 32. The number of adult fleas emerging from these eggs were counted 35 days after they were collected.

**Results:** Efficacy was calculated by comparing the development of eggs collected from fleas feeding on treated versus control animals. The data provided below represent the mean percent control for days 28 and 32 post-treatment. Since the drug is administered monthly, the critical parameter was determined to be efficacy at the end of a one month period. Because days 28 and 32 represent the final two egg collections of the month, the mean percent control from these two days was used to determine efficacy.

| Treatment Group<br>mg/kg | Mean % Control<br>Days 28 and 32 |
|---|---|
| Minimum of 20<br>(avg. 28.7) | 96.8 |

**Conclusions:** Lufenuron, administered at a minimum of 20 mg/kg body weight, was effective (>90%) in preventing flea egg development as measured at the end of a one month period (days 28 and 32). However, based on the data generated in corroborative dose titration studies #2 and #3, this dose was found to be inferior to the minimum effective dose of 30 mg/kg.

**Adverse Reactions**: None reported

**B. WELL-CONTROLLED CLINICAL FIELD TRIALS**

Lufenuron suspension was evaluated in a multi-centered, well-controlled clinical field trial conducted in twenty-one veterinary clinics located in several geographic locations. A list of the clinical investigators participating in the field trials can be found in Tables 1 and 2 below. Each study site conducted a trial using both cats and dogs (representing cat only households and mixed cat and dog households) and adhered to one of two study regimen protocols; Regimen I (corroborative study) evaluated lufenuron suspension in animals with low or no pre-existing flea infestations or Regimen II (pivotal study) which evaluated lufenuron suspension in animals with pre-existing flea infestations.

TABLE 1 CLINICAL INVESTIGATORS (REGIMEN II)

Pivotal Study

| | |
|---|---|
| Dr. Maynard Clark<br>Lafayette, CA | Dr. Perry Smith<br>Miami, FL |
| Dr. Bill Craig<br>San Antonio, TX | Dr. Jan Strother<br>Hartselle, AL |
| Dr. Dan McIlhany<br>San Antonio, TX | Dr. Tim Sung<br>Hercules, CA |
| Dr. Jim Raab<br>Fort Pierce, FL | Dr. Herb Utgard<br>North Miami Beach, FL |
| Dr. Doug Riley<br>Arlington, TX | Dr. Charles Ward<br>Carrboro, NC |

TABLE 2 CLINICAL INVESTIGATORS (REGIMEN I)

Corroborative Study

| | |
|---|---|
| Dr. Bill Bledsoe<br>Spartanburg, SC | Dr. Bill Paramore<br>Carmel, IN |
| **Dr. Jere Colley<br>**Dr. Gary Hunt<br>Opelika, AL | Dr. Ann Parker<br>Fayetteville, NC |
| Dr. Richard Devries<br>Albany, NY | Dr. Ken Schoolmeester<br>Dr. Karen Kennedy<br>Greensboro, NC |
| Dr. M. K. Jacobsen<br>Indianapolis, IN | Dr. Virgil Tongish<br>Westerville, OH |
| Dr. Joe Kinnarney<br>Reidsville, NC | Dr. Todd Schadler<br>Columbus, OH |
| Dr. Walter Legg<br>Lewisville, TX | |

** Due to a "Light" Flea Season, Only the Colley-Hunt Location Evaluated Flea Numbers High Enough for Acceptance in Data Analysis.<>/p>

Nine different breeds of cats were enrolled in the clinical trial with either domestic shorthair or domestic longhair breeds being most common.

During the course of the trials, no treatment-related deaths or adverse reactions were attributed to lufenuron. Isolated cases of vomiting occurred but were not consistent for any specific animal, breed, dose, treatment or placebo group, and, therefore, not attributed to lufenuron. Lufenuron was administered concurrently with a wide range of routinely used veterinary medications and vaccines without any adverse reactions reported. Two cats enrolled in the study (1 in the control group and 1 in the treated group) were found dead by their owners but the cause of these deaths were not determined.

The results of the pivotal study (Regimen II) will be discussed first, followed by the corroborative study (Regimen I).

*PIVOTAL CLINICAL FIELD TRIAL (Regimen II)*

**Type of Study:** Two-group, double blind, positive-controlled study designed to evaluate efficacy of lufenuron suspension in cats with established fleas infestations.

**Test Groups:** Group C received monthly lufenuron suspension plus monthly adulticide treatment (Adams(TM) Flea & Tick Mist) and Group D received monthly placebo suspension plus monthly topical methoprene and pyrethrin (Ovitrol Plus®).

**Number of Veterinary Clinics Participating:** Ten

**Animals:** Animals used in this study were recruited from households which were characterized "cat only" and had one or more cats and no dogs, or from households designated "mixed" which had at least one cat and one dog at the residence. Each investigator recruited six cat-only and six mixed households for the study which were randomly assigned to one of the two treatment groups. All animals from a household were enrolled in the same treatment group. Dogs from mixed households were treated with lufenuron tablets, which is the subject of a separate new animal drug application (PROGRAM® Tablets, NADA 141-035).

The following table displays the number of cats that were enrolled in and completed (parenthesis) the study:

| | Cats |
|---|---|
| Lufenuron | 114 (75) |
| Control | 93 (75) |

The age and weight ranges of the cats per treatment group at enrollment and completion (parenthesis) are provided below:

| Weight | Lufenuron | Control | Age | Lufenuron | Control |
|---|---|---|---|---|---|
| Up to 5 lbs. | 1 (1) | 3 (3) | < 6 mo. | 3 (3) | 2 (2) |
| 5.1 to 10 lbs | 74 (47) | 39 (32) | 6 mo. – 10 yrs. | 94 (59) | 85 (68) |
| > 10 lbs. | 39 (27) | 51 (40) | > 10 yrs. | 17 (13) | 6 (5) |

Only 3 cats < 6 months of age were treated with lufenuron in the study. Data to support the use of lufenuron in kittens < 6 months of age were generated in the pivotal target animal safety studies (see pages 24-32). In Pivotal Study D (see pages 30-31), the kittens were 11-12 weeks of age when treatment with lufenuron was initiated. In Pivotal Study E (see pages 31-32) the kittens were 6 weeks of age at the start of the study. The six week old kittens in this study weighed between 0.4 and 1.1 lbs when treatment was initiated.

**Study Duration:** Minimum of 6 months. In clinical field trial locations experiencing a "light" flea season (as determined by the clinical investigators based on their experience), the study protocol was amended to extend the study past six months.

**Dosage Administration:** Lufenuron suspension unit dose packs were administered to animals enrolled in Group C once-a-month for a minimum of six consecutive months. A topical flea adulticide was applied at the veterinary clinic at the time of the monthly flea count.

The clinical trials were initiated using a minimum effective dose of 20 mg/kg lufenuron, which was supported by initial studies (see corroborative efficacy studies, pages 9-13). Additional data suggested that the dose of 20 mg/kg was sub-optimal (see corroborative efficacy studies, pages 7-9). As soon as this information was known, a protocol amendment was implemented which changed the dosage administered to cats from 20 mg/kg to 30 mg/kg. As a result, from February 23 to May 20, 1990, the dose administered to cats was 20 mg/kg and from May 21, 1990, cats were dosed at 30 mg/kg.

**Controls:** The control (D) group cats in this trial received a placebo administered by the pet owner in a dosage form identical to lufenuron suspension, and were treated monthly with a topical, positive control insect growth regulator, methoprene [Ovitrol Plus®, (methoprene and pyrethrin)] per label instructions by the veterinary staff of the clinic.

**Clinical Evaluation:** At enrollment, all animals were given a complete physical examination and blood was collected for a complete blood count (CBC) and serum chemistry profile. As an initial treatment for the existing infestations and to assure compliance in the early stages of the study, households from both groups used weekly, on-animal pyrethrin adulticide applications (Adams(TM) Flea & Tick Mist ) for the first eight weeks of the study. Flea counts were performed in the clinic prior to treatment and monthly, thereafter. A short acting adulticide (Adams(TM) Flea & Tick Mist) was used as labeled once-a-month in the lufenuron-treated group to kill fleas for removal and counting. The control group received Ovitrol Plus®, which also contains a topical adulticide, once-a-month in the clinic to kill adult fleas for removal and counting. At the conclusion of the study, a final flea count and physical exam was performed. Blood was also collected for a CBC and serum profile.

**Concomitant Therapy:** Other than those treatments mentioned above, no other flea treatments to animals or their environment were allowed. Other types of medications commonly used in veterinary practice were allowed as needed.

**Results:** Lufenuron suspension was evaluated in animals with pre-existing infestations of fleas. Of the 207 cats enrolled under this protocol regimen, 114 comprised the lufenuron treatment group and 93 the control group. These animals represented a total of 81 households; 35 in the lufenuron group and 46 in the control group. A total of 151 cats were accepted into data analysis: 75 from the lufenuron group and 76 from the control group. At month 6, 150 animals remained in the trial; 75 in the lufenuron group and 75 in the control group. Descriptive statistics presented for all evaluation time points through six months are presented below for both lufenuron and control groups:

*Descriptive Statistics Regimen II*

| Month | Number of Cats Group C/Lufenuron | Mean Flea Counts |
|---|---|---|
| 0 | 75 | 22.28 |
| 1 | 75 | 8.76 |
| 2 | 75 | 9.32 |
| 3 | 75 | 9.77 |
| 4 | 75 | 3.84 |
| 5 | 75 | 2.91 |
| 6 | 75 | 4.03 |

| Month | Number of Cats Group D/Control | Mean Flea Counts |
|---|---|---|
| 0 | 76 | 18.21 |
| 1 | 76 | 5.74 |
| 2 | 76 | 2.47 |
| 3 | 76 | 1.92 |
| 4 | 76 | 1.61 |
| 5 | 76 | 1.49 |
| 6 | 76 | 1.11 |

**Statistical Analysis**: Non-parametric, one-way analyses of variance were used to analyze Savage scores, based on monthly flea counts (see Table 3 below). The positive control and lufenuron treatment groups were compared at each time period. The data were analyzed by household types: cat only, mixed or combined. No differences in Savage scores were found in mixed pet households, but differences were found in cat only households in months 2, 4, and 5. Differences were also found in Savage scores when combining households in months 2, 3, 4, and 6. Average flea counts were higher in lufenuron treated cats than in positive control cats from month 1 onwards (see Table 4 below).

Table 3

| | P-values using Savage Scores | | | | | | |
|---|---|---|---|---|---|---|---|
| Household | Initial Count | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 |
| Cats only | 0.7308 | 0.0807 | 0.0132 | 0.0882 | 0.0202 | 0.0353 | 0.0653 |
| Mixed | 0.1332 | 0.3826 | 0.1996 | 0.4048 | 0.873 | 0.48 | 0.6154 |
| Combined | 0.1956 | 0.0666 | 0.0025 | 0.0365 | 0.0136 | 0.1285 | 0.0454 |

Table 4

| | | Mean Flea Counts | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Household | Treatment | Initial Counts | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 |
| Cats only | Lufenuron | 18.40 | 8.17 | 12.21 | 13.92 | 5.00 | 3.77 | 5.02 |
| | Control | 20.11 | 4.83 | 2.42 | 2.47 | 1.78 | 1.06 | 1.06 |
| Mixed | Lufenuron | 29.19 | 9.81 | 4.19 | 2.41 | 1.78 | 1.37 | 2.26 |
| | Control | 16.50 | 6.55 | 2.53 | 1.43 | 1.46 | 1.88 | 1.15 |
| Combined | Lufenuron | 22.28 | 8.76 | 9.32 | 9.77 | 3.84 | 2.91 | 4.03 |
| | Control | 18.21 | 5.74 | 2.47 | 1.92 | 1.61 | 1.49 | 1.11 |

Each monthly administration of the positive control topical treatment (Ovitrol Plus®) occurred at the clinic by the veterinary staff, which may not represent typical pet owner practice and results.

**Conclusions**: In this well-controlled clinical trial, lufenuron suspension was effective in controlling flea populations when treatment was initiated during active infestations. Analyzing both cat-only and mixed cat and dog households, lufenuron reduced the mean flea count on 75 cats from approximately 22 to 4 after six monthly doses. This represents a reduction in the mean flea count of 82% from month 1 to month 6. In comparison, on 76 cats treated with a topical positive control, the mean flea count was reduced from approximately 18 to 1 after 6 months (94% reduction). While both lufenuron and the positive control reduced the mean number of fleas on these cats, there was more variability around the means each month in the lufenuron-treated group. The maximum number of fleas found on any one cat in the lufenuron group at the end of month 6 was 112 compared to 15 in the positive control group.

While the response to lufenuron was more variable than the response to the positive control, both products effectively reduced the mean number of fleas on the cats in this study. Considering the routes of administration between lufenuron (oral) and the positive control (topical), this difference between treatment groups is acceptable since there are no other oral flea control products currently available for use in cats.

*CORROBORATIVE CLINICAL FIELD TRIAL (Regimen I)*

**Type of Study:** Two group, double-blind, placebo-controlled study designed to evaluate the effect of lufenuron suspension under "pre-infestation" conditions.

**Test Groups:** Group A received lufenuron suspension and Group B received placebo suspension.

**Number of Veterinary Clinics Participating:** Eleven

**Animals:** Animals used in this study were recruited from households which were characterized "cat only" and had one or more cats and no dogs, or from households designated "mixed" which had at least one cat and one dog at the residence. Each investigator recruited six cat-only and six mixed households for the study which were randomly assigned to one of two treatment groups. All animals from a household were enrolled in the same treatment group. Dogs from mixed households were

treated with lufenuron tablets, which is the subject of a separate new animal drug application (PROGRAM® Tablets, NADA 141-035).

**Study Duration:** Minimum of six months. In clinical field trial locations experiencing a "light" flea season (determined by the clinical investigators based on their experience), the study protocol was amended to extend the study past six months.

**Dosage Administration:** Lufenuron suspension unit dose packs were administered to animals enrolled in Group A once-a-month for a minimum of six consecutive months. A topical flea adulticide was applied a the veterinary clinic at the time of the monthly flea count.

The clinical trials were initiated using a minimum effective dose of 20 mg/kg lufenuron, which was supported by initial studies (see corroborative efficacy studies, pages 9-13). Additional data suggested that the dose of 20 mg/kg was sub-optimal (see corroborative efficacy studies, pages 7-9). As soon as this information was known, a protocol amendment was implemented which changed the dosage administered to cats from 20 mg/kg to 30 mg/kg. As a result, from February 23 to May 20, 1990, the dose administered to cats was 20 mg/kg and from May 21, 1990, cats were dosed at 30 mg/kg.

**Controls:** Placebo suspension formulated without active ingredient was administered to Group B animals once-a-month for six consecutive months or longer if a particular study site used an extended protocol. The same number of placebo suspension unit dose packs were administered per animal weight range as in Group A. A topical flea adulticide was applied at the veterinary clinic at the time of the monthly flea count.

**Clinical Evaluation:** At enrollment all animals were given a complete physical examination and blood was collected for a complete blood count (CBC) and serum chemistry profile. Flea counts were performed in the clinic prior to treatment and monthly, thereafter, for the duration of the study. A short-acting adulticide (Adams(TM) Flea & Tick Mist) was used in both groups as labeled, once-a-month to kill adult fleas for removal and counting. At the conclusion of the study, a final flea count and physical exam were performed. Blood was also collected for a complete blood count and serum profile.

**Concomitant Therapy:** Other than once-a-month administration of the investigational drug, placebo and adulticide, no other flea treatments to animals or their environments were allowed. Other treatments and medications commonly used in the practice of veterinary medicine were allowed.

**Results:** Lufenuron was evaluated in animals before the onset of flea infestations. Of the 228 cats enrolled under this regimen, 116 comprised the lufenuron treatment group and 112 the placebo treatment group. These animals represented a total of 127 cat households, 65 in the lufenuron and 62 in the placebo groups, respectively. A total of 176 cases completed the trial and were *initially* entered into data analysis: 93 in the lufenuron treatment group and 83 in the placebo treatment group.

However, due to the fact that flea counts from 10 of 11 clinical trial locations in both lufenuron and placebo control groups were unacceptably low (due to a "light" flea season), data from those sites were not entered into final analysis. Only 27 cats (14

lufenuron and 13 placebo control) from the Colley-Hunt clinic were used in statistical analysis.

The study design allowed those households which developed intolerable flea infestations to withdraw from the study after the fourth month exam. This was necessary especially for Group B (placebo control) where severe flea infestations developed without adequate control measures. Some households withdrew from the study for other reasons including inconvenience in adhering to the protocol. Data analysis was performed only on data through the six month exam to prevent the data from becoming skewed by households with heavier flea infestations withdrawing from the study and households with fewer fleas remaining on trial.

Descriptive statistics presented for all evaluation time points through six months are presented below for both lufenuron and placebo treated groups:

Descriptive Statistics (Colley-Hunt Clinic)

| Month | Number of Cats Group A/Lufenuron | Mean Flea Counts |
|---|---|---|
| 0 | 14 | 1.14 |
| 1 | 14 | 6.00 |
| 2 | 14 | 2.29 |
| 3 | 14 | 6.43 |
| 4 | 14 | 19.57 |
| 5 | 14 | 16.14 |
| 6 | 14 | 16.21 |

| Month | Number of Cats Group B/Placebo | Mean Flea Counts |
|---|---|---|
| 0 | 13 | 0.62 |
| 1 | 13 | 3.38 |
| 2 | 13 | 41.69 |
| 3 | 13 | 168.38 |
| 4 | 13 | 509.31 |
| 5 | 13 | 1,547.31 |
| 6 | 5 | 322.40 |

**Statistical Analysis**: Non-parametric, one-way analyses of variance were used to analyze Savage scores, based on monthly flea counts (see Table 5). The placebo and lufenuron treatment groups were compared at each time period. The data were analyzed by household types: cat only, mixed pet or combined. Results were similar for each household type. Significant differences in Savage scores were found between treatment groups from month 2 onwards ($p < .05$). Average flea counts were lower in lufenuron treated cats than in placebo treated cats from month 2 onwards (see Table 6).

Due to lufenuron's mode of action as an insect development inhibitor (IDI), a difference in performance between lufenuron-treated (Group A) and placebo-treated (Group B) animals was not expected for approximately 60 days post-treatment.

Table 5

| | P-values using Savage Scores | | | | | | |
|---|---|---|---|---|---|---|---|
| Household | Initial Count | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 |
| Cats only | 0.4655 | 0.6101 | 0.0014 | 0.0014 | 0.0014 | 0.0014 | * |
| Mixed | 0.9999 | 0.9999 | 0.0366 | 0.0371 | 0.0366 | 0.0371 | 0.0371 |
| Combined | 0.3818 | 0.609 | 0.0002 | 0.0002 | 0.0002 | 0.0002 | 0.0004 |

* 8 cats removed from the study due to heavy flea infestations.

Table 6

| | | Mean Flea Counts | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Household | Treatment | Initial Counts | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 |
| Cats only | Lufenuron | 1.60 | 8.40 | 2.10 | 8.20 | 24.60 | 20.50 | 16.30 |
| | Control | 1.00 | 5.50 | 59.75 | 199.00 | 707.00 | 2387.75 | * |
| Mixed | Lufenuron | 0.00 | 0.00 | 2.75 | 2.00 | 7.00 | 5.25 | 16.00 |
| | Control | 0.00 | 0.00 | 12.80 | 119.40 | 193.00 | 202.60 | 322.40 |
| Combined | Lufenuron | 1.14 | 6.00 | 2.29 | 6.43 | 19.57 | 16.14 | 16.21 |
| | Control | 0.62 | 3.38 | 41.69 | 168.38 | 509.31 | 1547.31 | 322.40 * |

*8 cats were removed from the study due to heavy flea infestations.

**Conclusions**: Lufenuron was effective in preventing the development of flea populations on cats when compared to a placebo control, though evaluable data from enough geographic locations and enough animals were not generated to make this study pivotal or to support a claim for the prevention of flea populations. These data were generated at only one clinic location in Alabama with 14 cats in the lufenuron group and 13 in the placebo group.

**C. DOSAGE FORM ACCEPTABILITY STUDY**

*Lufenuron Suspension: Evaluation of Dosage Form Acceptability in Cats*.

**Purpose:** To evaluate the acceptability of lufenuron suspension when administered orally to cats either directly into the mouth or indirectly, by mixing into food.

**Investigator:**

Jan K. Strother, DVM
North Alabama Cat and Bird Veterinary Clinic
Hartselle, AL

**Dosage Form:**

Lufenuron 7% Suspension
Aluminum tube dispenser

**Study Design:** Thirty healthy client-owned cats (13 males and 17 females) ranging in age from 2.5 months to 13 years and ranging in weight from 2 pounds 8 ounces to 15 pounds were recruited for this study. Animals previously enrolled in lufenuron clinical trials were not allowed into this study. As animals were enrolled, they were given a routine physical exam, weighed and randomly assigned to one of the following three primary treatment groups:

*Treatment Group A (n = 17): Indirect Oral Administration in Food by the Pet Owner*

The pet owner was instructed to dose the animal by placing lufenuron suspension in the cat's wet food. If the dosage form was determined to be unacceptable or unable to be administered by this route, the pet owner was instructed to contact the principal investigator and make arrangements for secondary evaluation by direct oral administration into the mouth.

*Treatment Group B (n = 6): Direct Oral Administration by Mouth in the Clinic by the Principal Investigator*

The investigator was instructed to evaluate direct oral administration in the clinic by squeezing the entire contents of the appropriate sized lufenuron suspension unit dose pack into the mouth of the cat. If the dosage form was determined to be unacceptable by this route, the principal investigator was instructed to provide the pet owner lufenuron suspension for secondary evaluation of acceptability by administration in the food at home (within 72 hours of primary evaluation).

*Treatment Group C (n = 7) Direct Oral Administration by Mouth in the Clinic by the Pet Owner*

In this group, the principal investigator was instructed to evaluate direct oral administration of lufenuron suspension administered by the pet owner in the clinic. If the dosage form was determined to be unacceptable or not able to be administered, the principal investigator was instructed to provide the pet owner lufenuron suspension for secondary evaluation of acceptability by administration in the food at home (within 72 hours of primary evaluation).

**Evaluation:** Acceptability was evaluated by observation of how the cat responded to oral administration of lufenuron suspension either directly into the mouth or indirectly by mixing into the animal's food. Parameters to be evaluated were specific acceptability problem indicators such as excessive salivation or spitting upon administration of the drug. If dosing problems prevented administration by the primary route assigned, the secondary evaluation route was to be evaluated.

**Results:** Twenty-eight of thirty cats administered lufenuron oral suspension by one of three primary routes evaluated accepted their entire dose without spitting, salivating, food refusal or other dosage acceptance problems. Two cats described by their owners as finicky eaters did not eat their food, which was the primary route of administration for those two animals. Both cats were successfully dosed by direct oral administration in the clinic by the principal investigator as the secondary route of evaluation. Data from this study is summarized in the following table:

Number of Cats Accepting Dose by

| Food/Group A | Mouth/Group B | Mouth/Group C |
|---|---|---|
| 15*/17 | 6/6 | 7/7 |
| | 2*/2 | |

* The two cats which did not accept treated food were successfully dosed by mouth in the clinic by the veterinarian.

**Conclusions**: Of the 30 privately-owned cats enrolled in this palatability study, only 2 cats did not accept the lufenuron suspension dose. The two cats that rejected the product were in the group evaluating the acceptability of the product when mixed with canned (wet) cat food. All attempts to administer the product directly into the cats' mouths by either the veterinarian or the cat owners were successful.

The unit dose pack used in this study was an aluminum tube. Since this study was conducted, the unit dose pack has been changed to a flexible pouch design. Because the ability of the veterinarian and cat owners to administer the product directly into the cats' mouths using this flexible pouch has not been tested, the product has been labeled for use only when mixed in the cats' food.

## III. TARGET ANIMAL SAFETY

Five pivotal target animal safety studies were conducted in cats to address the tolerance and safety of lufenuron. These studies were designed to evaluate safety of the drug administered at exaggerated doses in breeding animals, in adult cats, in kittens and in combination with topically applied flea adulticides. These studies demonstrated that lufenuron suspension provides a wide therapeutic index when administered orally to cats at the minimum recommended dose of 30 mg/kg body weight, monthly. A list of target animal safety studies, principal investigators and study sites can be found in the following Table 7.

TABLE 7 PIVOTAL TARGET ANIMAL SAFETY STUDIES

| Study Type | Study Director | Study Location |
|---|---|---|
| 1) 90-Day Oral Toxicity | Drs. E. Chow<br>D. S. Wyand | Ciba-Geigy Corp<br>Farmington, CT |
| 2) Reproduction Study | Dr. James Laveglia | FDRL*<br>Waverly, NY |
| 3) Acute Oral Toxicity Study (Tolerability) in Young Cats | Dr. Edwin Goldenthal | IRDC**<br>Mattawan, MI |
| 4) Acute Oral Toxicity Study (Tolerability) in Cats | Dr. Edwin Goldenthal | IRDC**<br>Mattawan, MI |
| 5) Oral Safety Evaluation in Juvenile Cats | Dr. David Serrone | Ricerca, Inc.<br>Painesville, OH |

* Food and Drug Research Laboratories
** International Research and Development Corporation

## A. 90-Day Toxicity Study With Lufenuron in Cats

**Type of Study:** 90-day subchronic study designed to evaluate lufenuron used alone at exaggerated doses or in combination with topically applied flea control products.

**Investigator/Study Director:**

Dr. E. Chow
Dr. D. S. Wyand
Ciba-Geigy Corporation
Environmental Health Center
Farmington, CT

**Animals:** Seventy-eight domestic shorthair cats (39 males and 39 females), approximately 9 months of age and ranging in weight from 2.5 to 6.1 kg were used in this study.

**Dosage Form:** Lufenuron 7% Suspension

**Route of Administration:** Oral (by gavage). Dosing was performed in the morning prior to feeding. One tablespoon of canned cat food was given to each cat prior to and after the gavage procedure.

**Controls:** Placebo suspension made from excipients without active ingredient

**Dosage/Frequency of Treatment:** Nine groups of cats were formed; groups 1 - 4 were made up of 12 animals each (6 males and 6 females) and groups 5 - 9 were made up of 6 animals each (3 males and 3 females). The following table details the treatment(s) each group received:

| Group | Lufenuron Treatment | Commercial Insecticide |
|---|---|---|
| 1 | Placebo Suspension | None |
| 2 | 100 mg/kg | None |
| 3 | 300 mg/kg | None |
| 4 | 500 mg/kg | None |
| 5 | 500 mg/kg | Carbaryl/Once Weekly |
| 6 | 500 mg/kg | Pyrethrin/Every Two Weeks |
| 7 | 500 mg/kg | Propoxur/Once Weekly |
| 8 | Placebo Suspension | Pyrethrin/Every Two Weeks |
| 9 | Placebo Suspension | Propoxur/Once Weekly |

Lufenuron suspension was administered at either 100, 300, or 500 mg/kg for three consecutive days each month for three months (cumulative dose of 10, 30, and 50X the minimum recommended monthly dose of 30 mg/kg). The three classes of commercial insecticides used were applied per the maximum labeled rate, as follows:

- *Carbaryl (powder)*--the cats were dusted liberally with the powder once per week for a total of 13 applications.
- *Pyrethrin (spray)*--the cats were sprayed until damp once every two weeks for a total of 7 applications.

- *Propoxur (dip)*--The cats were dipped briefly into a diluted solution until the skin was wet once per week for a total of 13 applications. They were lightly patted with an absorbent towel to remove excess solution before being placed back into cages.

**Study Duration:** Three Months

**Evaluation:** Criteria evaluated for treatment effect included observations for overt toxicity, mortality, body weights, food consumption, ophthalmologic examination, hematological, biochemical and urinalysis determination, and macroscopic and microscopic examination of tissues including selected major organ weights. A complete necropsy was performed on all cats at termination.

**Results:** Administration of lufenuron alone at up to 500 mg/kg 3 times per month for 3 months (cumulatively 50X the monthly use rate) or in combination with topical flea adulticide products resulted in no adverse effects as measured by clinical or ophthalmoscopic observation, body weight change or food/water consumption. There were no deaths.
During weeks 5 and 9, an increase in GGT activity was observed in males exposed to lufenuron alone at 500 mg/kg or in combination with topical insecticide products. However, there were no apparent treatment-related body weight changes or associated histopathologic findings in the livers.

**Conclusions:** Lufenuron administered to young adult cats at doses up to 17X the minimum recommended monthly dose (cumulative monthly dose up to 50X the minimum recommended monthly dose) elicited no evidence of toxicological effects.

**B. A Clinical Reproduction Study in Cats With Lufenuron**

**Type of Study:** The objective of this laboratory study was to evaluate the effects of lufenuron on reproductive functions in male and female cats.

**Investigator:**

Dr. James Laveglia
Food and Drug Research Laboratories
Waverly, NY

**Animals:** Six adult male and 36 adult female cats, weighing between 2.5 and 4.8 kg, were assigned to two groups of 3 males and 18 females per group. All animals used were sexually mature and proven breeders.

**Dosage Form:** Lufenuron 7% Suspension

**Controls:** Placebo suspension comprised of formulation excipients without active ingredient.

**Route of Administration:** Oral. The cats were fed *ad libitum* throughout the study.

**Dosage/Frequency of Treatment:** In order to ensure maximum exposure during all phases of embryogenesis, the drug was administered to treated cats at rates and intervals required to maintain a blood level greater than 3X the concentration

achieved following a 1X dose. This was achieved by administering 5 consecutive weekly doses of approximately 60 mg/kg body weight during the first 30 days, followed by single monthly doses of approximately 100 mg/kg through the remaining months of the study. The bred females were dosed throughout gestation and weaning. Males were dosed prior to mating and through breeding period. Control animals received suspension vehicle (placebo) only.
Blood samples were collected on approximately days 30, 90, 150 (1 week after queening), and 240 (1 week after weaning from both queens and kittens).

**Mating:** Cats were assigned randomly to two study groups, Group 1: Placebo treated and Group 2: Lufenuron treated, by stratified randomization according to body weight. The first 6 females assigned to Group 1 were placed in a pen with the first male assigned to Group 1. This assignment continued in groups of 6 animals until 18 females and 3 males were assigned to each of the two study groups.
When the females were visibly larger with increased body weights suggesting pregnancy, they were moved from the breeding pens and placed in individual cages.
**Study Duration:** Approximately 8 Months

**Evaluation:** Specific parameters evaluated were survival rate, appearance and behavior, body weight changes, food consumption, male and female fertility indices, mean gestation period, kitten viability, growth and survival.

**Results:** No compound-related differences were noted in regard to physical condition, mortality, maternal or kitten body weights, clinical laboratory parameters, mating indices or viability of offspring between the two groups (see Table 8).

Table 8

| Group | Male Fertility Index fertile males/total males mated | Female Fertility Index gravid females/total females mated | Queening Index #live kittens/ #gravid females | Gestation Index #live litters/ #gravid females |
|---|---|---|---|---|
| Control | 3/3 (100%) | 14/18 (78%) | 36/14 (2.57) | 13/14 (93%) |
| Treated | 3/3 (100%) | 13/18 (72%) | 37/13 (2.84) | 12/13 (92%) |

The mean blood concentrations of lufenuron from days 30 and 90 ranged from 225 to 1019 ng/mL, with a mean of 453 ng/mL. A single 30 mg/kg dose of lufenuron in cats produced an average blood concentration of 75 ng/mL (see corroborative safety study C, page 33). Therefore, blood levels in this reproductive safety study were maintained in excess of the targeted 3X concentration. Blood samples taken from both kittens and queens 1 week after weaning showed that the concentration of lufenuron was consistently higher in kittens than in the queens. The blood concentration ratio (kitten:queen) ranged from 1.3 to 6.4 with an average of 3.3.

One treated male died while on study. This animal exhibited decreased activity, unsteady gait, anorexia, vomiting and emaciation prior to death. Upon microscopic examination of the tissues, death was attributed to subacute foreign body inhalation and chronic fibrosing nephritis. Both conditions were determined to have existed prior to study initiation. A variety of observations such as sores, scratches, hair loss, scabs, and vaginal discharge were seen evenly distributed between control and treated

groups and were considered "normal" in a cat breeding colony and indicative of social behavior during estrus and breeding.

No malformed kittens were observed in the treated group; however, two control kittens had 6 digits on the front paws and three control kittens had flattened rib cages. A total of 11 kittens in the control group were stillborn or died during the lactation period and a total of 13 kittens in the treated group were stillborn or died during the lactation period. The number of kittens surviving to weaning was 30 in the control group and 32 in the treated group. No treatment-related effects were noted.

**Conclusions:** Administration of lufenuron to breeding cats at exaggerated doses (cumulatively 10X for one month and 3.3X for 6 months) demonstrated that there were no treatment-related effects on the reproductive or kitten health parameters measured.

**C. Acute Oral Toxicity Study (Tolerability) in Young Cats with Lufenuron**
**Type of Study:** The objective of this study was to evaluate the acute oral toxicity of lufenuron to young cats administered a single exaggerated dose equivalent to 10X the monthly use rate.

**Study Director:**
Dr. Edwin Goldenthal
International Research & Development Corporation
Mattawan, Michigan

**Animals:** Twelve domestic shorthair kittens (6 males and 6 females) 11-12 weeks of age, ranging in weight from 1 to 1.2 kg, were used in this study. The 12 animals were assigned to 2 groups of 6 animals each (3 males and 3 females). The kittens were housed 3 per cage based on sex and treatment group.

**Dosage Form:** Lufenuron 7% Suspension

**Controls:** Placebo suspension containing formulation excipients without active ingredient.

**Route of Administration:** Oral

**Dosage/Frequency of Treatment:** Lufenuron was administered in a single oral dose to achieve 300 mg/kg (10X the minimum recommended monthly dose). A control group received placebo suspension in an identical manner.

**Study Duration:** Fifteen Days Post Treatment

**Evaluation:** Mortality, clinical signs, body weights, hematological, clinical chemistry and clinical pathology were the criteria evaluated for treatment effects.

**Results:** All cats survived to study termination. There were no test article-related effects observed during the study period nor were there any changes or differences in body weights. There were no test article-related changes observed in hematological parameters. One male kitten in the 300 mg/kg group had a slightly elevated total bilirubin value (0.4 mg/dl) compared to the mean value in the control group (0.2 mg/dl) 24 hours after treatment, but this value had returned to normal by day 15.

Another male kitten in the treated group showed elevated GGT activity of 6 IU/L at 24 hours when compared to the mean control value of 1 IU/L. This value was down to 1 IU/L by day 15.

**Conclusion:** Lufenuron, when administered as a single dose, equivalent to 10X the recommended use rate did not reveal any marked toxic effects.

**D. Acute Oral Toxicity Study (Tolerability) in Cats with Lufenuron**

**Type of Study:** The objective of this study was to evaluate the acute oral toxicity of lufenuron to cats administered a single elevated dose equivalent to 10X the recommended monthly use rate.

**Study Director:**

Dr. Edwin Goldenthal
International Research & Development Corporation
Mattawan, Michigan

**Animals:** Twelve domestic short hair cats (6 males and 6 females) 7 months of age and ranging in weight from 2.2 to 5.1 kg were used in this study. The 12 animals were assigned to 2 groups of 6 animals each (3 males and 3 females). The cats were individually housed.

**Dosage Form:** Lufenuron 7% Suspension

**Controls:** Placebo suspension containing formulation excipients without active ingredient.

**Route of Administration:** Oral

**Dosage/Frequency of Treatment:** Lufenuron was administered in a single oral dose to achieve 300 mg/kg (10X the minimum recommended monthly dose). A control group received placebo suspension in an identical manner.

**Study Duration:** Fifteen Days Post Treatment

**Evaluation:** Mortality, clinical signs, clinical pathology, body weights, hematological and clinical chemistry criteria were evaluated for treatment effect.

**Results:** All cats survived to study termination. No test article-related effects were observed during the study period nor were there any marked changes or differences in body weights. No test article-related changes were observed in hematological, biochemical or urological parameters.

**Conclusion:** Lufenuron, when administered as a single dose, equivalent to 10X the recommended use rate did not reveal any toxic effects.

**E. An Oral Safety Evaluation In Juvenile Cats with Lufenuron (Starting with Nursing Animals and Proceeding to Young Adults)**

**Type of Study:** The objective of this study was to evaluate the safety of lufenuron suspension administered at multiples of the minimum recommended dose to kittens 6 weeks of age for 5 months.

**Study Director/Location:**

Dr. David M. Serrone
Ricerca, Inc.
Painesville, Ohio

**Animals:** Twelve male and 12 female domestic shorthair kittens, 6 weeks of age and ranging in weight from 181 to 453 grams, were used in this study. The 24 animals were assigned to 4 groups of 6 animals each (3 males and 3 females). Initially, the animals were housed as litters with their queens. After weaning at 8 weeks of age each kitten was placed in an individual cage.

**Dosage Form:** Lufenuron 7% Suspension

**Controls:** Placebo suspension containing formation excipients without active ingredient.

**Route of Administration:** Oral. Following weaning at 8 weeks of age, the test material was given with food.

**Dosage/Frequency of Treatment:** Lufenuron suspension was administered for three consecutive days on each of five consecutive months to three groups of animals at doses of 40, 120 and 200 mg/kg body weight (representing 1.3, 4, and 6.7X the minimum recommended dose of 30 mg/kg) The cumulative doses administered *monthly* were 4X, 12X and 20X the minimum recommended monthly dose of 30 mg/kg. Placebo suspension was administered based on volumes of the high dose of lufenuron suspension (200 mg/kg).

**Study Duration:** Five Months

**Evaluation:** Criteria evaluated for treatment effect included observations for overt toxicity, mortality, body weights, food consumption, ophthalmologic examinations, hematological, biochemical and urinalysis determinations, and macroscopic and microscopic examination of tissues, including selected major organ weights.

**Results:** One high dose male died and one high dose female was sacrificed in extremis during Week 8. Neither death was attributed to test material administration. The only gross finding at necropsy in the high dose male was an empty digestive tract. Histologic lesions were limited to the hematopoietic system. There was almost total lymphoid depletion of lymph nodes and spleen. The thymus consisted solely of stroma with no apparent lymphoid stem cells. Bone marrow was severely hypocellular. The pathologist concluded that the lack of stem cells in the thymus suggested a failure of embryonic development rather than a hypoplastic change from postnatal causes. The high dose female had a deformed rib cage, which was considered a primary factor in the cause of death and a moderate chronic pneumonia. No clinical observations were seen at the postdosing period in either male or female animals receiving the test material. There were no compound-related oculopathies seen at the eye examination.

There were no differences in body weight or body weight gains for any of the study animals when compared to controls. Mean food consumption values for both male and female animals receiving test material were comparable to controls. No differences were observed in hematology values when groups receiving test material were compared to controls. Urinalysis values did not indicate any test material-related effect.

At necropsy, no observations were made which were considered to be related to the administration of the test material. Mean absolute liver weights for high dose males (121.820 grams) and low dose females (75.303 grams) were higher when compared to controls (97.163 g and 65.040 g, for the male and female controls, respectively). These findings were not considered to be compound related because no identifiable histopathologic effects were observed.

**Conclusion:** Administration of lufenuron to 6 week old kittens at doses of 40, 120 and 200 mg/kg body weight for three consecutive days a month for five consecutive months (which represents a cumulative dose of 4X, 12X and 20X the recommended use rate), did not induce any test article-related changes in any of the parameters evaluated in this study. One high dose male died with histologic lesions noted in the hematopoietic system (lymphoid depletion). Mean absolute liver weights for the high dose males and low dose females were higher when compared to controls.

***CORROBORATIVE STUDIES***

A. *28-Day Rangefinding Study with Lufenuron in Cats*

**Investigator/Study Director:** Dr. Kenneth L. Pavkov

**Study Location:**

Ciba-Geigy Corporation
Farmington, CT

**Animals:** Two male and 2 female domestic shorthair cats, 6 months of age and weighing between 2.5 and 2.9 kg, were used in this study.

**Dosage Form**: Lufenuron 15% Suspension

**Dosage/Frequency of Treatment:** Lufenuron was administered via syringe to the back of the mouth once daily for 29 consecutive days at a dose of 100 mg/kg/day. The cats were dosed within 2 to 4 hours after feeding. Male cat #1 and female cat #3 were dosed for an additional 3 weeks. On study days 28 and 36, these two cats were treated topically with a permethyrin dip. On study days 43 and 50, these two cats were treated topically with a chlorpyrifos dip. Cats #1 and #3 were necropsied on day 52 while cats #2 and #4 were necropsied on day 29.

**Results**: During the first 29 days of the study, there were no clinical signs or effects on body weight observed for any of the 4 treated cats. Average food consumption fell slightly during the 4 weeks from 178 grams/day during week 1 to 146 grams/day during week 4. For cats #1 and #3, treatment-related effects were evident during the continuation of the study. Body weights remained static, however food consumption

fell from 138 grams/day during week 4 for cats #1 and #3 to 48 grams/day during week 7. Cat #1 showed the following clinical signs following the second chlorpyrifos dip--salivation, ataxia, diarrhea, disorientation, emesis, pallor, hypothermia, dehydration, bloat, splayed hindlimbs, and convulsions. This cat became moribund on study day 52. At necropsy, cat #1 showed pallor, dehydration, and reddened kidneys. Necropsy results for the other 3 cats were normal.

B. *4-Week Rangefinding Study with Lufenuron in Cats*

**Investigator/Study Director:** S. M. MacAskill

**Study Location:**

Ciba-Geigy Corporation
Farmington, CT

**Animals:** Eight female domestic shorthair cats, 6 months of age and weighing between 2.1 and 2.7 kg were used in this study. The cats were divided into two groups; 4 received placebo and 4 received lufenuron.

**Dosage Form**: Lufenuron 7% Suspension

**Dosage/Frequency of Treatment:** The cats were treated with either placebo or lufenuron at 100 mg/kg/day for 3 consecutive days per week for 4 weeks.

**Results**: All animals appeared clinically normal throughout the study. There was no effect on body weight or food consumption during the 4 week study.

C. *28-Day Absorption Study in Cats with Lufenuron*

**Investigator/Study Director:** Dr. James Laveglia

**Study Location:**

Food and Drug Research Laboratories
Waverly, NY

**Animals:** Six adult female domestic shorthair cats, ranging in age from 2 to 10 years and weighing between 2.5 and 2.8 kg, were used in this study.

**Dosage Form**: Lufenuron 7% Suspension

**Dosage/Frequency of Treatment:** Each cat was treated once with a minimum dose of 30 mg/kg. Blood samples were taken prior to treatment, 48 hours after dosing and 7, 14, 21, and 28 days after dosing.

**Results**: There were no clinical signs of toxicity observed during this study. The following table (Table 9) shows the blood concentrations of lufenuron measured in this study. The average blood concentration for the 28 day period was 75 ng/mL.

Table 9--Blood Concentrations of Lufenuron

| | CAT TATTOO NUMBER | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | UB6 | IAT4 | IDJ3 | IOH1 | PP4 | MA4 | Mean |
| -1 | ND | ND | ND | ND | ND | ND | 0 (0) |
| 2 | ND | 184 | 185 | 96 | 81 | 47 | 99 (74) |
| 7 | ND | 137 | 132 | 86 | 64 | 31 | 75 (55) |
| 14 | ND | 171 | 117 | 82 | 73 | 39 | 80 (60) |
| 21 | ND | 140 | 119 | 73 | 62 | 24 | 69 (54) |
| 28 | ND | 128 | 127 | 67 | 57 | 34 | 69 (51) |
| AUC (ng/mL) | 0 | 4091 | 3536 | 2172 | 1812 | 911 | 2087 (15) |
| Ave Conc. (ng/mL) | 0 | 146 | 126 | 78 | 65 | 33 | 75 (55) |

## IV. HUMAN FOOD 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 which are non-food animals.

## V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that PROGRAM® Suspension (lufenuron), when used under labeled conditions of use, is safe and effective. The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in understanding that this drug works to control flea populations by inhibiting flea egg development. If the product is used without knowledge of the flea's life cycle and without the knowledge of which topical flea adulticides are required and when they should be used, the drug will not work effectively.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(c)(2)(F)(ii)), this approval qualifies for 3 years of marketing exclusivity beginning on the date of approval because it contains reports of new clinical or field investigations, other than bioequivalence or residue studies, essential to the approval and conducted or sponsored by the applicant.

## VI. LABELING (Attached)

1. Package Inserts
   - Veterinarian's Insert
   - Owner's Insert
2. Flexible Pouch (unit dose pack)--135 mg and 270 mg
3. Carton--135 mg and 270 mg
4. Carton Display Package--135 mg and 270 mg

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.