Approval Date: March 31, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-105

B. Sponsor

Novartis Animal Health US, Inc.

C. Proprietary Name

Program 6 Month Injectable for Cats

D. Established Name

Lufenuron 10% Sterile Suspension Injectable

E. Dosage Form(s), Route of Administration and Recommended Dosage

Program 6 Month Injectable for Cats is injected subcutaneously once every 6 months, at the recommended minimum dosage of 10 mg/kg (4.54 mg/lb) of lufenuron.

Recommended Dosage Schedule

Body weight	Syringe Size	Lufenuron Dose
Up to 8.8 lbs (Up to 4.0 kg)	Small (0.4 mL)	40 mg
8.9 lbs to 17.6 lbs (4.1 to 8.0 kg)	Large (0.8 mL)	80 mg

F. Dispensing Status

Prescription

G. Indication

Program 6 Month Injectable for Cats is indicated for use in cats, six weeks of age and older, for the control of flea populations. Lufenuron controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of insecticides may be necessary for adequate control of adult fleas.

II. EFFECTIVENESS

Lufenuron is an insect development inhibitor which breaks the flea life cycle at the egg stage. The adult female 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 which forms the exoskeleton of larvae.

A. Dose Establishment

Two studies, one titration and one confirmation, were conducted to establish and confirm the minimum effective dose of lufenuron for the control of flea populations. These studies titrated and confirmed a one-time minimum dose of 10 mg/kg for cats for 6 months duration.

1. Dose Titration Study

Purpose: Different doses of lufenuron injectable were compared to determine the 6 month efficacy for control of reproduction in the cat flea.

Investigator: Byron Blagburn, Ph.D.

Study Location: Auburn University, Auburn, Alabama

Type of Study: Experimental infestation with *Ctenocephalides felis*

Animals: Forty domestic short hair cats (20 males, 20 females), 5 to 7 months of age, were divided into five groups of eight animals each.

Dosage Groups:

Group 1: 2.5 mg/kg lufenuron

Group 2: 5.0 mg/kg lufenuron

Group 3: 10.0 mg/kg lufenuron

Group 4: 20.0 mg/kg lufenuron

Group 5: Placebo (formulation excipients without active ingredient)

Route of administration: Subcutaneous Injection

Frequency of Treatment: One injection

Duration of study: Cats were experimentally infested with 100 cat fleas periodically from Day -8 through Day 193. Flea eggs were collected from each cat periodically from Day -4 through Day 196. The number of adult fleas emerging from these eggs were counted. Efficacy was based on the cumulative percent control of flea egg hatch from Day 14 through Day 182 (6 months).

Results: Presented in the following table are the cumulative percent controls for Days 14 through 182.

Cumulative Percent Control From Day 14 Through Day 182

Treatment Group	Day 14 – Day 182
2.5 mg/kg	15.0%
5.0 mg/kg	63.1%
10.0 mg/kg	94.8%
20.0 mg/kg	98.3%

Cumulative percent control of ³ 90% was achieved in the 10 mg/kg group from Day 14 post-injection. Efficacy of ³ 90% was achieved in each sampling in this group from Day 21 post-treatment and persisted until the end of the study. The data indicated that the 10 mg/kg dose of injectable lufenuron suspension is the minimum effective dose for effective control of flea populations for 6 months post-treatment. A two to three week induction phase post-injection should be expected before adequate control is achieved.

Conclusions: Lufenuron injectable was effective (³ 90%) in inhibiting development of *C. felis* at a minimum dose of 10 mg/kg from 2-3 weeks post-injection through 6 months post-injection.

Adverse Reactions: Palpable lumps at the injection sites were observed in cats from all groups treated with lufenuron beginning within 3 days after injection and persisting through Day 24. Less common reactions included vocalization during injection, licking the injection site and blood at the injection site.

2. Dose Confirmation Study

Purpose: To confirm that the dose of 10 mg/kg of lufenuron injectable provides 180 days control of reproduction of *C. felis* on cats.

Investigator: Byron Blagburn, Ph.D.

Study Location: Auburn University- Auburn, Alabama

Type of Study: Experimental infestation with C. felis

Animals: Twenty domestic shorthair cats (10 males, 10 females), 5 to 17 months of age, were divided into two groups of 10 cats each.

Doses Tested:

Group 1: Minimum of 10.0 mg/kg lufenuron
Group 2: Placebo (saline)

Route of administration: Subcutaneous injection

Frequency of treatment: One injection

Duration of study: Cats were experimentally infested with 100 cat fleas periodically from Day -8 through Day 178. Flea eggs were collected from each cat periodically from Day -3 through Day 182. The number of adult fleas

emerging from these eggs were counted. Efficacy was based on the cumulative percent control from Day 14 through Day 182.

Results: The cumulative percent control from Days 14 through 182 was 97.7%.

Efficacy of ³ 90% was achieved in each sampling from Day 28 post-treatment and persisted until the end of the study.

Conclusions: Lufenuron at the minimum recommended dose of 10 mg/kg was effective (³ 90%) in inhibiting development of *C. felis* from 2-3 weeks post-injection through 6 months post-injection.

Adverse Reactions: Palpable lumps at the injection sites were observed on cats treated with lufenuron beginning 3 days after injection and persisting through Day 38.

B. Clinical Trial

General Clinical Trial

Purpose: To evaluate the safety and efficacy of Program 6 Month Injectable for Cats in clinical use for the control of flea populations.

Investigators/Study Locations:

Dr. Edward Aycock
Lewisville North Animal Clinic
121 Degan
Lewisville, TX 75067

Dr. Anita Genova
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920 E. Main Street
Palmyra, PA 17078

Dr. Ralph Barrett
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Dr. Clay Glenn
East Orlando Animal Hospital
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Orlando, FL 32822

Dr. John Basterfield
Juan DeFuca Veterinary
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Dr. Jim Harris
Clinic Palmetto Animal Hospital
2221 Second Loop Road
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Dr. Jay Butan
Canal Animal Hospital
501 24th Avenue
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Dr. Richard Johnson
Broadway Animal Hospital
North 380 Broadway
El Cajon, CA 92021

Dr. Bill Craig
Ingram Park Animal Hospital Towne
6603 Ingram Road
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Dr. Dan McIlhany
North Animal Hospital
13335 San Pedro Avenue
San Antonio, TX 78216

Dr. Tom Elston
Cat Hospital of Irvine
14429 Culver Drive
Irvine, CA 92714

Dr. Jim Raab
Tri-County Animal Hospital
1807 Okeechobee Road
Fort Pierce, FL 34950

Dr. Tod Schadler
Great Southern Animal Hospital
2685 South High Street
Columbus, OH 43207

Dr. Elaine Wexler-Mitchell
Cat Care Clinic
2638 North Tustin Avenue
Orange, CA 92665

Dr. Ken Schoolmeester
Jamestown Veterinary Hospital
720 Guilford College Road
Greensboro, NC 27410

Dr. Judy Vaeth
183 Animal Hospital

1010 West Airport Freeway
Irving, TX 75062

Dr. Jan Strother (Site 1)
N. Alabama Cat & Bird
Veterinary Clinic
Route 4, Box 92
Hartselle, AL 35640

Dr. Jan Strother (Site 2)
N. Alabama Cat & Bird Veterinary Clinic
7900 Bailey Cove Road
Huntsville, AL 35802

Type of Study: Natural infestations of fleas in pet cats.

Animals: Four hundred sixty-six client owned cats were enrolled in the study. A total of 294 were treated with lufenuron and 102 were treated with placebo. All were included in the safety analysis. A total of 183 cats were treated with lufenuron and used to evaluate the efficacy of lufenuron injectable for the control of flea populations.

Data from seventy cats were not included in the efficacy analysis due to the fact that they had violated the study protocol. These protocol deviations included: cats spending more than 6 hours outdoors, untreated animals visiting the premises, treated cats having contact with stray animals, addition of untreated pets in the household during the study, owners moving to new and potentially infested locations, owners using other insecticides regularly and pets being mis-dosed with placebo instead of lufenuron.

Dosage Form: Program 6 Month Injectable Suspension

Route of administration: Subcutaneous injection

Dose Tested: Lufenuron at a minimum of 10 mg/kg

Frequency of Treatment: One injection every 6 months

Control: Monthly flea counts on cats treated with lufenuron were compared to the initial flea counts, thus the animals served as their own control. The placebo-treated cats in this study served to document the existence of flea infestations in the same geographic areas as the treated cats and were not included in any statistical analyses.

Duration of study: The cats were given two injections, six months apart. Efficacy data were collected by combing fleas from the animal at the initial visit and every month thereafter. The final flea count was made 1 month after the second injection (Month 7).

Results: The following table shows the monthly mean flea counts, standard deviations and numbers of animals included in the analysis from the initial visit to month 6

	Initial Visit	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
Mean	43.3	34.1	24.1	17.5	16.4	13.6	11.3
StDev	63.6	57.2	45.1	32.1	38.3	30.4	34.8
N	183	180	178	169	164	156	149

The cats were placed into two categories depending upon the percent control relative to their initial visit flea count. The two categories were < 75% control and ³ 75% control. Results of Fisher's exact test indicate significant differences ($p < 0.5$) between month 1 and succeeding months.

Conclusions: These data indicate that Lufenuron 6 Month injectable for Cats effectively controls flea populations on cats.

Adverse Reactions: The following table compares the percentages of cats treated with lufenuron injectable compared to the placebo (saline) control that exhibited the following clinical observations.

Injection Site	**Lufenuron Injection** **N = 294**	**Placebo Injection** **N = 102**
Pain on injection, tenderness, twitching or fractious during injection	16%	4.0%
Lump or granuloma	8.5%	1.0%
Vomiting	2.5%	0.6%
Listlessness/Lethargy	1.9%	0.6%
Diarrhea	1.3%	1.1%
Anorexia	1.1%	0.4%

Two injection site lumps removed from cats treated with lufenuron showed changes on histologic examination. In one cat the lump showed evidence of inflammation surrounding an area of necrosis. There was marked proliferation of fibrous connective tissue accompanying this reaction. In the other cat, the lump showed granulomatous inflammation which included non-pleomorphic fibrocytes and fibroplasia.

III. TARGET ANIMAL SAFETY

A. Acute Safety (Tolerability) Study in Cats with a Lufenuron Injectable Formulation.

Purpose: To evaluate the safety of Program 6 Month Injectable for Cats when given at 10X the projected use rate.

Investigator: Edwin I. Goldenthal

Study Location: MPI Research, Mattawan, MI

Type of Study: Laboratory safety study,

Animals: Twelve (6 males, 6 females) domestic shorthair cats, 6 months of age, were divided into 2 groups of 6 cats each.

Dosage Groups:

Group 1: Program 6 Month Injectable for cats

Group 2: Placebo injection (saline)

Route of administration: Subcutaneous injection

Dose Tested: Minimum dose of 100 mg/kg

Frequency of Treatment: Once (divided into 10 injections of 0.4 mL each)

Duration of study: The animals were observed twice daily for signs of mortality and morbidity for a two week observation period following dosing. Physical examinations were conducted prior to dosing and prior to necropsy at week 2. Individual body weights were recorded weekly. Clinical pathology evaluations (hematological, biochemical and urological) were conducted on all animals pre-test and at study termination. Complete necropsies were conducted on each cat.

Results: All animals survived to the scheduled necropsy. The only test article-related clinical findings observed during the study were raised hard areas at the injection sites in 4/6 cats treated with lufenuron. Test article-related macroscopic findings were limited to the injection site in animals given lufenuron. White foreign material, presumed to be deposits of lufenuron, was seen within the subcutaneous tissue of the injection sites of all animals treated with lufenuron. The macroscopic findings were consistent with the gross findings and included mild to severe granulomatous inflammation and trace to moderate acute inflammation.

Conclusions: Program 6 Month Injectable for Cats is safe when administered subcutaneously to cats at doses up to 10X the recommended dose. The drug causes inflammation at the site of injection.

B. Two Month Safety Study in Kittens Beginning at Two Weeks of Age with a Lufenuron Injection Formulation.

Purpose: To evaluate the safety of Program 6 Month injectable for cats when given at up to 3X the projected use rate to kittens.

Investigator: Edwin I Goldenthal

Study Location: MPI Research, Mattawan, MI

Type of study: Laboratory safety study

Animals: Seventy (36 males, 34 females) 2-week old domestic shorthair kittens were divided into three groups. The placebo group had 24 kittens assigned while the 1X and 3X group had 23 kittens each. The kittens remained with the lactating queens until weaning was completed.

Dosage Groups:

Group 1: Placebo Injection (saline)

Group 2: Program 6 Month Injectable at 1X

Group 3: Program 6 Month Injectable at 3X

Route of Administration: Subcutaneous injection

Doses Tested:

1X: Lufenuron at a minimum of 10 mg/kg
3X: Lufenuron at a minimum of 30 mg/kg

Frequency of treatment: Two treatments, approximately 4 weeks apart on Day 1 and Day 29.

Duration of Study: All kittens were observed twice daily for signs of morbidity and mortality for the 2 month study. Observations included clinical signs, body weight (weekly), hematology, serum chemistry, ophthalmic exams, gross pathology and organ weights. Complete necropsies were conducted on all kittens.

Results: One queen cannibalized all three males in her litter and injured one of the female kittens. The injured female was euthanized due to her injuries. All other kittens survived to study termination. Small raised areas at the injection site (presumed to be deposits of lufenuron) were observed in all but 3 kittens receiving lufenuron. Two kittens in the 1X group and 2 in the 3X group had a scabbed area and/or scar at the injection site which dissipated within 1 week.

White foreign material, presumed to be a depot of lufenuron, was seen macroscopically within subcutaneous tissue of 80% of the kittens treated with lufenuron. The histologic findings were consistent with the gross findings and included granulomatous inflammation, acute inflammation, fibrosis and occasional mineralization.

Conclusions: Program 6 Month Injectable for Cats is safe when administered subcutaneously to kittens at doses up to 3X the recommended dose. The drug causes inflammation at the site of injection.

C. Six Month Safety Study in Cats with a Lufenuron Injectable Formulation

Purpose: To evaluate the safety of Program 6 Month Injectable for Cats when given at doses up to 5X the recommended use rate to cats for six months.

Investigator: Edwin I. Goldenthal

Study Location: MPI Research, Mattawan, MI

Type of Study: Laboratory safety study

Animals: Forty-eight (24 males, 24 females) 2 month old domestic shorthair cats were divided into four groups of 12 cats each.

Dosage Groups:

Group 1: Placebo Injection (saline)

Group 2: Program 6 Month Injectable for Cats at 1X

Group 3: Program 6 Month Injectable for Cats at 3X

Group 4: Program 6 Month Injectable for Cats at 5X

Route of Administration: Subcutaneous injection

Doses Tested:

1X: Lufenuron at a minimum of 10 mg/kg

3X: Lufenuron at a minimum of 30 mg/kg

5X: Lufenuron at a minimum of 50 mg/kg

Frequency of Treatment: Three treatments, approximately every 2 months (on Day 1 and Weeks 8 and 16), were given in 3 different areas (left and right flank and scruff of the neck) in order to evaluate resolution of injection site reactions.

Duration of study: All animals were observed twice daily for mortality and signs of overt toxicity during the 6 month study. Clinical examinations and body weights were conducted weekly. Ophthalmic and physical examinations were conducted pretest and at study termination. Hematological and biochemical evaluations were conducted pretest and monthly, and urological examinations were conducted monthly after the second month.

Complete necropsies were conducted on all cats.

Results: One male cat (control group) died immediately after blood collection on day 121. It did not recover from anesthesia. All other cats survived to study termination. Small raised areas at the injection site were observed in all cats receiving lufenuron immediately after injection and persisted in some cases for the duration of the study. One or more treated cats showed some minor irritation at the injection site which dissipated within 2 weeks.

An increase in the number of Heinz body inclusions was observed in the 5X dose group at months 3-6. No other test article-related hematological or biochemical findings were noted. Macroscopically, deposits of white foreign material (presumed to be the lufenuron), were found in the subcutaneous tissues of most treated cats at the injection sites. Microscopically, the injection sites showed evidence of granulamatous inflammation, acute inflammation, fibrosis and occasionally the presence of vacuolated macrophages and/or mineralization. Older injection sites (from the Day 1 injection) had less inflammation and less test article present, which indicates these effects may resolve over time.

Conclusions: Program 6 Month Injectable for Cats is safe for use in cats and kittens 8 weeks of age and older at doses up to 5X the recommended dose. The drug causes inflammation at the site of injection which appears to resolve over time.

IV. HUMAN 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 of the Implementing regulations. The data demonstrate that Program 6 Month Injectable for Cats (lufenuron 10% sterile suspension), 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 the administration of this injectable dosage form.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, 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 and studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

Patent Information: #4,798,837 (expires January 2006), 5,416,102 (expires May 2012), and 5,420,163 (expires May 2012).

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.