Date of Approval: November 13, 2024

# FREEDOM OF INFORMATION (FOI) SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-502

revolution® PLUS

(selamectin and sarolaner topical solution)

Cats

This supplement provides for the addition of the indication for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

Sponsored by:

Zoetis Inc.

## Executive Summary

revolution® PLUS (selamectin and sarolaner topical solution) is approved for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater. revolution® PLUS is an antiparasitic drug that is administered topically using the supplied applicator tubes.

revolution® PLUS is already approved to prevent heartworm disease caused by *Dirofilaria immitis*; treat and control roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections; treat and control ear mite (*Otodectes cynotis*) infestations; kill adult fleas (*Ctenocephalides felis*); treat and prevent flea infestations; and treat and control tick infestations with *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), and *Ixodes scapularis* (black-legged tick) for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

### Safety and Effectiveness

The sponsor conducted two laboratory studies to show that revolution® PLUS prevents *D. caninum* infections in cats. In each study, the cats were experimentally infested on Days 0, 7, 14, 21, and 30 with adult fleas that were infected with *D. caninum*. On Day 0, revolution® PLUS was applied to cats in the treatment groups and a vehicle control was applied to cats in the control groups. The vehicle control contained all the inactive ingredients in revolution® PLUS but contained no selamectin or sarolaner. Flea counts were performed on Day 33 (72 hours after the last flea infestation), and on Day 58 the cats were humanely euthanized and necropsied for recovery of *D. caninum*. Scolex counts were performed on Day 58 or 59. The scolex is the attachment organ of the tapeworm that anchors the parasite to the host's intestinal wall.

In both studies, revolution® PLUS was greater than 94% effective at killing adult fleas and over 97% effective at preventing *D. caninum* infections. In one study, 100% (10/10) of cats in the treatment group had no fleas, and in the other study, 90% (9/10) of cats in the treatment group had no fleas, while all cats in both control groups remained infested on Day 33. On Day 58 or 59, cats in both treatment groups had lower scolex counts compared to cats in the control groups. No adverse reactions related to revolution® PLUS were reported in either study.

The FOI Summary for the original approval of revolution® PLUS, dated November 9, 2018, contains a summary of target animal safety studies for cats.

### User Safety

The labeling for revolution® PLUS includes safety information for people who handle or administer the drug. People, including children, should not touch the application site on the treated cat for 4 hours after the dose is applied.

### Conclusions

Based on the data submitted by the sponsor for the approval of revolution® PLUS, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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# I. GENERAL INFORMATION

## A. File Number

NADA 141-502

## B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

## C. Proprietary Name

revolution® PLUS

## D. Drug Product Established Name

selamectin and sarolaner topical solution

## E. Pharmacological Category

Antiparasitic

## F. Dosage Form

Topical Solution

## G. Amount of Active Ingredient

60 mg/mL selamectin
10 mg/mL sarolaner

## H. How Supplied

revolution® PLUS is available in 0.25 mL, 0.5 mL, or 1 mL applicator tubes in cartons containing 1, 3, or 6 tubes.

## I. Dispensing Status

Prescription (Rx)

## J. Dosage Regimen

The recommended minimum dosage is 2.7 mg selamectin per pound (6.0 mg/kg) of body weight in combination with 0.45 mg sarolaner per pound (1.0 mg/kg) of body weight administered monthly.

## K. Route of Administration

Topical

### L. Species/Class

Cats

### M. Indication

revolution® PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*, the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. revolution® PLUS kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat, and the treatment and control of tick infestations with *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), and *Ixodes scapularis* (black-legged tick) for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

### N. Effect of Supplement

This supplement provides for the addition of the indication for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

## II. EFFECTIVENESS

The effectiveness of revolution® PLUS for the prevention of *Dipylidium caninum* infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat was demonstrated in two well-controlled laboratory studies (A186C-ZA-21-270 and A186C-US-23-294) described below. These studies demonstrated that revolution® PLUS is effective for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

### A. Dosage Characterization

This supplemental approval does not change the previously approved dosage of 2.7 mg selamectin per pound (6.0 mg/kg) of body weight in combination with 0.45 mg sarolaner per pound (1.0 mg/kg) of body weight administered monthly. The FOI Summary for the original approval of NADA 141-502 dated November 9, 2018, contains dosage characterization information for cats.

### B. Substantial Evidence

1. Laboratory Dose Confirmation Study A186C-ZA-21-270

   **Title:** Prevention of *Dipylidium caninum* Infections in Cats as a Direct Result of Killing *Ctenocephalides felis* on Cats. (Study No. A186C-ZA-21-270)

   **Study Dates:** June 30, 2022, to April 8, 2024

**Study Location:** Bloemfontein, South Africa

**Study Design:**

Objective: To evaluate the effectiveness of revolution® Plus for the prevention of *Dipylidium caninum* infection by killing the flea intermediate host in cats for one month when administered at a minimum dosage of 2.7 mg selamectin per pound (6.0 mg/kg) of body weight in combination with 0.45 mg sarolaner per pound (1.0 mg/kg) of body weight in cats with induced infestations of *Ctenocephalides felis*.

Study Animals: Twenty domestic shorthair cats (12 males and 8 females), 16 to 113 months of age, and 2.8 to 4.7 kg body weight.

Experimental Design: This study was a vehicle-controlled, masked, randomized complete block study design. Cats were randomly assigned to the vehicle control group (10 cats) or the revolution® PLUS group (10 cats). Each cat was infested with approximately 100 *D. caninum*-infected *C. felis* fleas on Days 0, 7, 14, 21, and 30. Fleas were counted and removed on Day 33. The study was conducted in accordance with Good Clinical Practice (GCP) guidance.

**Table II.1. Treatment Groups for Study A186C-ZA-21-270**

| Treatment Group | Treatment | Day of Treatment | Cats per Group | Days of Flea Infestation | Days of Flea Count | Day of Scolex Count |
|---|---|---|---|---|---|---|
| T01 | Vehicle control | Day 0 | 10 | Days 0, 7, 14, 21, and 30 | Day 33 | Day 59 |
| T02 | revolution® PLUS | Day 0 | 10 | Days 0, 7, 14, 21, and 30 | Day 33 | Day 59 |

Drug Administration: All treatments were applied topically to the skin at the base of the neck directly in front of the shoulder blades on Day 0. The vehicle control contained all the inactive ingredients in revolution® PLUS but contained no selamectin or sarolaner.

Measurements and Observations: General health observations were conducted at least once daily. Clinical observations and administration site evaluations were conducted prior to treatment on Day 0 and at 1, 3, 6, and 24 hours after treatment. Administration sites were also evaluated on Days 3, 5, and 58. Fleas were counted and removed on Day 33. On Day 58, the cats were humanely euthanized and necropsied for recovery of *D. caninum*. Scoleces were counted on Day 59.

**Statistical Methods:**

Flea Counts: The flea counts were analyzed with a generalized linear mixed model with a fixed effect of treatment and random effects of room and block within room. Least squares mean (LSM) counts were reported by treatment group. Comparison of mean flea counts was conducted between the revolution® PLUS group and the control group using contrasts at the (two-sided) 5%

significance level.

Percent effectiveness of the revolution® PLUS group with respect to the control group was calculated using LSM with the formula [(C – T) / C] X 100, where C = LSM of flea counts for the control group and T = LSM of flea counts for the revolution® PLUS group.

Scolex Counts: The scolex counts were transformed with a natural logarithm transformation prior to analysis with a general linear mixed model. The model contained the fixed effect of treatment and the random effects of room and block within room. Geometric mean was obtained through back-transformation of the LSM estimated from the model. Comparison of mean scolex counts was conducted between the revolution® PLUS group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the revolution® PLUS group with respect to the control group was calculated using LSM with the formula [(C – T) / C] X 100, where C = geometric mean of scolex counts for the control group and T = geometric mean of scolex counts for the revolution® PLUS group.

**Results:**

Flea Counts: The control group met the definition for adequate flea infestation with at least 6 of the 10 cats having ≥ 50 fleas following the final flea infestation on Day 30.

The mean flea count for the revolution® PLUS group was significantly different compared to the control group on Day 33 (P<0.0001), demonstrating 100% effectiveness against fleas.

**Table II.2. Day 33 LSM flea counts and percent effectiveness against fleas for Study A186C-ZA-21-270**

| Control Group LSM Flea Count | revolution® PLUS LSM Flea Count | Percent Effectiveness |
|---|---|---|
| 96.2 | 0 | 100% |

Scolex Counts: The control group met the definition for adequate infection with at least 6 of the 10 cats having ≥ 2 scoleces at necropsy.

There was a significant difference in mean scolex counts (P = 0.0046) for revolution® PLUS -treated cats compared to the control group, demonstrating 97.1% effectiveness for the prevention of *D. caninum* infection.

**Table II.3. Day 59 scolex counts and percent effectiveness for the prevention of *Dipylidium caninum* infections for Study A186C-ZA-21-270**

| Control Group Geometric Mean Scolex Count | revolution® PLUS Geometric Mean Scolex Count | Percent Effectiveness |
|---|---|---|
| 12.9 | 0.4 | 97.1% |

**Adverse Reactions:** No treatment related adverse reactions were reported in this study.

**Conclusions:** A single topical treatment of revolution® PLUS (1.0 mg/kg sarolaner + 6.0 mg/kg selamectin) was effective in preventing the infection of *D. caninum* as a direct result of killing the vector flea, *C. felis*, on the treated cats for one month.

2. Laboratory Dose Confirmation Study A186C-US-23-294

**Title:** Prevention of *Dipylidium caninum* Infections in Cats as a Direct Result of Killing *Ctenocephalides felis* on Cats. (Study No. A186C-US-23-294)

**Study Dates:** June 20, 2023, to April 10, 2024

**Study Location:** Waverly, NY

**Study Design:**

Objective: To evaluate the effectiveness of revolution® Plus for the prevention of *Dipylidium caninum* infection by killing the flea intermediate host in cats for one month when administered at a minimum dosage of 2.7 mg selamectin per pound (6.0 mg/kg) of body weight in combination with 0.45 mg sarolaner per pound (1.0 mg/kg) of body weight in cats with induced infestations of *Ctenocephalides felis*.

Study Animals: Twenty domestic shorthair cats (10 males and 10 females), 8 to 47 months of age, and 2.7 to 7.7 kg body weight.

Experimental Design: This study was a vehicle-controlled, masked, randomized complete block study design. Cats were randomly assigned to the vehicle control group (10 cats) or the revolution® PLUS group (10 cats). Each cat was infested with approximately 100 *D. caninum*-infected *C. felis* fleas on Days 0, 7, 14, 21, and 30. Fleas were counted and removed on Day 33. The study was conducted in accordance with GCP guidance.

**Table II.4. Treatment Groups for Study A186C-US-23-294**

| Treatment Group | Treatment | Day of Treatment | Cats per Group | Days of Flea Infestation | Days of Flea Count | Day of Scolex Count |
|---|---|---|---|---|---|---|
| T01 | Vehicle control | Day 0 | 10 | Days 0, 7, 14, 21, and 30 | Day 33 | Day 58 |
| T02 | revolution® PLUS | Day 0 | 10 | Days 0, 7, 14, 21, and 30 | Day 33 | Day 58 |

Drug Administration: All treatments were applied topically to the skin at the base of the neck directly in front of the shoulder blades on Day 0. The vehicle control contained all the inactive ingredients in revolution® PLUS but contained no selamectin or sarolaner.

Measurements and Observations: General health observations were conducted at least once daily. Clinical observations and administration site evaluations were conducted prior to treatment on Day 0 and at 1, 3, 6, and 24 hours after treatment. Administration sites were also evaluated on Days 3, 5, and 58. Fleas were counted and removed on Day 33. On Day 58, the cats were humanely euthanized and necropsied for recovery of *D. caninum* and counting of scoleces.

**Statistical Methods:**

Flea Counts: The flea counts were analyzed with a generalized linear mixed model with a fixed effect of treatment and a random effect of block. LSM counts were reported by treatment group. Comparison of mean flea counts was conducted between the revolution® PLUS group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the revolution® PLUS group with respect to the control group was calculated using LSM with the formula [(C – T) / C] X 100, where C = LSM of flea counts for the control group and T = LSM of flea counts for the revolution® PLUS group.

Scolex Counts: The scolex counts were transformed with a natural logarithm transformation prior to analysis with a general linear mixed model. The model contained the fixed effect of treatment and the random effect of block. Geometric mean was obtained through back-transformation of the LSM estimated from the model. Comparison of mean flea counts was conducted between the revolution® PLUS group and the control group using contrasts at the (two-sided) 5% significance level.

Percent effectiveness of the revolution® PLUS group with respect to the control group was calculated using LSM with the formula [(C – T) / C] X 100, where C = geometric mean of scolex counts for the control group and T = geometric mean of scolex counts for the revolution® PLUS group.

**Results:**

Flea Counts: The control group met the definition for adequate flea infestations with at least 6 of the 10 cats having ≥ 50 fleas following the final flea infestation on Day 30.

The mean flea count for the revolution® PLUS group was significantly different compared to the control group on Day 33 (P = 0.0001), demonstrating 94.3% effectiveness against fleas.

**Table II.5. Day 33 LSM flea counts and percent effectiveness against fleas for Study A186C-US-23-294**

| Control Group LSM Flea Count | revolution® PLUS LSM Flea Count | Percent Effectiveness |
|---|---|---|
| 56.3 | 3.2 | 94.3% |

Scolex Counts: The control group met the definition for adequate infection with at least 6 of the 10 cats having ≥ 2 scoleces at necropsy.

There was a significant difference in mean scolex counts (P < 0.0001) for revolution® PLUS -treated cats compared to non-treated controls, demonstrating 99.3% effectiveness for the prevention of *D. caninum* infection.

**Table II.6. Day 58 scolex counts and percent effectiveness for the prevention of *Dipylidium caninum* infections for Study A186C-US-23-294**

| Control Group Geometric Mean Scolex Count | revolution® PLUS Geometric Mean Scolex Count | Percent Effectiveness |
|---|---|---|
| 93.2 | 0.7 | 99.3% |

**Adverse Reactions:** No treatment related adverse reactions were reported in this study.

**Conclusions:** A single topical treatment of revolution® PLUS (1.0 mg/kg sarolaner + 6.0 mg/kg selamectin) was effective in preventing the infection of *D. caninum* as a direct result of killing the vector flea, *C. felis*, on the treated cats for one month.

## III. TARGET ANIMAL SAFETY

FDA did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-502 dated November 9, 2018, contains a summary of target animal safety studies for cats.

## IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

## V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to revolution® PLUS:

**Not for human use. Keep this and all drugs out of the reach of children.**

**Do not come into contact with or allow children to contact the application site until 4 hours post application.**

**In humans, REVOLUTION PLUS may be irritating to skin and eyes.** REVOLUTION PLUS, and selamectin topical solution contain isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Reactions such as hives, itching and skin redness have been reported in humans after accidental dermal contact with selamectin topical solution. Individuals with known hypersensitivity to selamectin topical solution should use caution or consult a health care professional before applying this product on a cat. **Wash hands after use and wash off any product in contact with the skin immediately with soap and water.** If contact with eyes occurs, then flush eyes copiously with water; if wearing contact lenses, rinse the eyes first then remove contact lenses and continue to rinse for 5 – 10 minutes and seek medical attention. In case of ingestion by a human,

contact a physician immediately. The safety data sheet (SDS) provides more detailed occupational safety information. For a copy of the SDS or to report a suspected adverse reaction, call Zoetis at 1-888-963-8471.

Flammable – Keep away from heat, sparks, open flames or other sources of ignition.

## VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that revolution® PLUS, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above.

### A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to monitor the safe use of the product, including treatment of any adverse reactions.

### B. Exclusivity

This supplemental approval for revolution® PLUS qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indication for the prevention of *Dipylidium caninum* (tapeworm) infections as a direct result of killing *Ctenocephalides felis* vector fleas on the treated cat.

### C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval did not require a reevaluation of certain safety or effectiveness data in the application.

### D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.