Date of Approval: May 23, 2024

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 131-675

Safe-Guard®

(fenbendazole)

Type A medicated article to be used in the manufacture of Type B and Type C medicated feeds

Wild quail

This supplement provides for the addition of wild quail with the indication for the treatment and control of *Aulonocephalus* spp. in wild quail.

Sponsored by:

Intervet Inc.

Executive Summary

Safe-Guard® (fenbendazole) 20% Type A medicated article is approved for the treatment and control of Gastrointestinal worms: Cecal worms, (*Aulonocephalus* species) in wild quail. A Type A medicated article is used to make Type B and Type C medicated feeds. Only a Type C medicated feed can be fed directly to animals.

Safety and Effectiveness

The sponsor conducted a field study to evaluate the effectiveness of Safe-Guard® (fenbendazole) 20% Type A medicated article to treat and control natural infections of cecal worms (*Aulonocephalus* spp.) in quail. Wild northern bobwhite quail had access to 12 treated and control feeding stations. The feeding stations were sufficiently far apart that, based on the known movement patterns of quail, the birds stayed near their respective feeding station. The 6 treated feeding stations contained medicated feed made from Safe-Guard® (fenbendazole) 20% Type A medicated article, and the 6 control feeding stations contained a non-medicated basal diet that met the birds' basic nutritional needs. Quail had unrestricted access to the feed for 21 days. At the end of the study, quail were trapped and then necropsied. Worms recovered from the ceca of quail were identified and counted. Safe-Guard® (fenbendazole) 20% Type A medicated article was 100% effective against natural infections with *Aulonocephalus* spp. No treatment-related adverse reactions were reported.

The sponsor conducted a margin of safety study in normal, healthy-appearing, commercially-bred, male and female quail. The birds were fed either a non-medicated basal diet or medicated feed made from Safe-Guard® (fenbendazole) 20% Type A medicated article at 1X, 2X, or 3X the labeled dose. The control and medicated feed were administered *ad libitum* for 63 to 67 consecutive days (3 times the labeled duration of 21 days). No clinically significant treatment-related findings were identified. The reproductive safety of Safe-Guard® (fenbendazole) 20% Type A medicated article in quail was not evaluated.

Human Food Safety

FDA evaluated the need to address the impact of fenbendazole on antimicrobial resistance among bacteria of public health concern in or on quail treated with Safe-Guard® (fenbendazole) 20% Type A medicated article. The drug 1) does not have properties that exert selection pressure for the development of resistant bacteria in food-producing animals; 2) is not used to treat gastroenteritis or other bacterial diseases in people; 3) is not being developed to treat a bacterial disease in people; and 4) is not used to treat a bacterial disease in food-producing animals. Therefore, FDA determined that a microbial food safety assessment was not required for the intended use of Safe-Guard® (fenbendazole) 20% Type A medicated article in quail.

FDA determined that it was not necessary to reassess the acceptable daily intake (ADI) for total residue of fenbendazole. FDA previously established the ADI as 40 µg/kg body weight per day and the safe concentrations in individual edible tissues as 4 parts per million (ppm) for muscle, 12 ppm for liver, 24 ppm for kidney, 24 ppm for fat or skin with fat, 0.64 ppm for milk, and 2.4 ppm for eggs. These values reflect the partition of the ADI between meat, milk, and eggs.

FDA did not require the sponsor to conduct new total residue and metabolism studies. Safe-Guard® (fenbendazole) 20% Type A medicated article is already approved for use in turkeys, and the target tissue, marker residue, and tolerance assigned for fenbendazole residues in turkeys (a related major species) were applied to fenbendazole residues in quail (a minor species). The target tissue is liver, the marker residue is fenbendazole sulfone, and the tolerance is 6 ppm in quail liver. FDA also did not require the sponsor to conduct new comparative metabolism studies. Comparative metabolism of fenbendazole residues in quail is also demonstrated by the previous comparative metabolism study in turkeys.

The sponsor conducted one tissue residue depletion study to assess the quantity and nature of the residues in tissues derived from quail treated with fenbendazole. FDA used the information from this study, in combination with the ADI and safe concentrations, to establish a zero-day withdrawal period in quail. FDA evaluated the analytical method for detecting fenbendazole residues and found its use acceptable.

FDA determined that there is a reasonable certainty of no harm for residues of fenbendazole in the edible tissues of treated quail following human consumption when Safe-Guard® (fenbendazole) 20% Type A medicated article is used according to the labeling.

Conclusions

Based on the data submitted by the sponsor for the approval of Safe-Guard® (fenbendazole) 20% Type A medicated article, 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 131-675

B. Sponsor

Intervet Inc.
126 E. Lincoln Ave.
Rahway, NJ 07065

Drug Labeler Code: 000061

C. Proprietary Name

Safe-Guard®

D. Drug Product Established Name

fenbendazole

E. Pharmacological Category

Anthelmintic

F. Dosage Form

Type A medicated article to be used in the manufacture of Type B and Type C medicated feeds

G. Amount of Active Ingredient

200 g/kg (90 g/lb)

H. How Supplied

25 lb bag

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

Wild quail: 90.7 g of fenbendazole/ton of Type C medicated feed, to be fed for 21 consecutive days

K. Route of Administration

Oral

L. Species/Class(es)

Wild quail

M. Indication

For the treatment and control of *Aulonocephalus* spp. in wild quail.

N. Effect of Supplement

This supplement provides for addition of wild quail with the indication for the treatment and control of *Aulonocephalus* spp. in wild quail.

II. EFFECTIVENESS

A. Dosage Characterization

Based on effectiveness information from published studies and pilot data generated for the use of fenbendazole 20% Type A medicated article against cecal worm (*Aulonocephalus* spp.) in quail, it was determined that 100 ppm (90.7 g/ton) for up to 21 consecutive days is the appropriate dosage for the treatment and control of *Aulonocephalus* spp. in wild quail.

B. Substantial Evidence

1. Field effectiveness study in northern bobwhite quail

   Title: The Efficacy of Fenbendazole-Treated Feed to Control Parasites in Wild Northern Bobwhite Quail. (Study No. 353-EFF-2016)

   Study Dates: July 2016 to September 2016

   Study Locations: Lubbock, TX and Mitchell County, TX

   Study Design:

   Objective: To evaluate the efficacy of fenbendazole against natural infections of cecal worms (*Aulonocephalus* spp.) in wild quail when administered as medicated feed at 100 ppm for 21 days, under field conditions.

   Study Animals: Wild northern bobwhite quail inhabiting the Spade Ranch in Mitchell County, TX had access to treated and control feeding stations. A total of 57 quail (30 treated and 27 control) were trapped, transferred to an aviary, and necropsied for parasite collection. All quail were approximately 4 months of age or older.

   Experimental Design: The experimental site was a linear tract of land approximately 18 miles in length. Within the tract of land, 12 feeding stations were arranged in a line. Stations 1 through 6 were each separated by one mile and feeding stations 6 and 7 were six miles apart. Feeding stations 7 through 12 were arranged in the same continuous line, also each separated by one mile. The 12 feeding stations were randomly assigned to treatment groups, six to the fenbendazole treated group and six to the control group. Feeding station was the experimental unit.

Study personnel involved in necropsy, worm counting, and worm identification were masked, and study personnel involved in treatment assignment and administration, and treatment feed manufacturing were not masked. This study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Table II.B.1 Treatment groups

Treatment groups	Treatment regimen	No. of quail collected per group	No. of feeding stations per treatment group
Control	Non-medicated feed	27	6
Treated	Medicated feed containing 100 ppm fenbendazole administered for 21 days	30	6

Drug Administration: Non-medicated basal diet was used as the control feed. The test article was mixed with the basal diet to prepare the Type C medicated feed containing 100 ppm fenbendazole. Twelve specifically designed feeding stations were used in the study. The stations were completely confined in an 8 x 8 x 6 ft covered enclosure with ground entrance holes and included a quail attractor component. The control or medicated feed were placed in a modified ground feeder and the feeder was kept in the center of the feeding station. Quail had unrestricted access to the feed.

Measurements and Observations: The control feed and Type C medicated feed were provided in control and treated feeding stations, respectively, from Days 1 to 21. Quail were trapped and collected on Days 22 and 23 and necropsied on Days 26 to 28. The criteria for effectiveness were worm counts during necropsy. Worms recovered from the ceca of quail were identified and counted. Quail were monitored for adverse events in the field and while housed at the aviary.

Statistical Methods: All analyses were performed using Statistical Analysis System (SAS). For each feeding station, the arithmetic mean worm count was calculated and then log-transformed prior to statistical analysis: log (arithmetic mean of station + 1). The log-transformed data were analyzed by a linear mixed model with treatment as the fixed effect. The hypothesis test was conducted as two-sided test at $\alpha = 0.05$.

Percent effectiveness was calculated as $100\times[(C-T)/C]$, where C was the geometric mean worm counts back-transformed from the Least Squares (LS) mean of the control group obtained from the statistical model and T was the geometric mean worm counts back-transformed from the LS mean of the treated group.

Results:

Table II.B.2 Comparisons of geometric means of worm counts in treated and control groups

Treatment	Number of feeding stations	Geometric mean*	Percent effectiveness (%)	P-value#
Control	6	65.74	-	-
Treated	6	0	100	<0.0001

*Geometric Mean was back-transformed from the LS means obtained from the statistical analysis.
#P-value was obtained from the comparison between the two treatment groups

Adverse Reactions: No test article-related adverse reactions were reported in this study.

Conclusions: This study demonstrates that fenbendazole 20% Type A medicated article, when administered orally in Type C medicated feed at approximately 100 ppm for 21 days to wild quail, was effective against natural infections with *Aulonocephalus* spp.

III. TARGET ANIMAL SAFETY

The effects of fenbendazole administered orally via medicated feed were evaluated in a margin of safety study conducted in quail. The objective of the study was to evaluate the safety of fenbendazole 20% Type A medicated article at 1X, 2X, and 3X (100, 200, and 300 ppm) the recommended label dose of 100 ppm (90.7 g/ton) in feed for 3 times (63 days) the recommended duration of treatment of 21 days. The reproductive safety of fenbendazole 20% Type A medicated article in quail was not evaluated.

A. Margin of Safety Study in Quail

Title: The Safety of Fenbendazole in Quail Fed Rations Containing 0, 100, 200, and 300 ppm Fenbendazole *ad libitum* for 63 days. (Study No. 353-TAS-2016)

Study Dates: August 2016 to October 2016

Study Location: Lubbock, TX

Study Design:

Objective: To evaluate the safety of fenbendazole in quail when administered at 1X, 2X, and 3X (100, 200, and 300 ppm) the recommended label dose of 100 ppm in feed for 3 times (63 to 67 days) the recommended duration of treatment of 21 days.

Study Animals: One hundred sixty commercially bred, mixed sex Northern bobwhite quail were used in the study. Normal healthy-appearing quail were enrolled in the study. The quail were approximately 56 days old when the dosing period started.

Experimental Design: The study was performed in compliance with Good Laboratory Practices (GLP) regulations (21 CFR Part 58) as a randomized, controlled, and masked margin of safety study. Study personnel who performed daily activities and necropsy were masked to the treatment. Quail were fed medicated feed containing 100, 200, or 300 ppm fenbendazole or control feed *ad libitum* for a period of 67 days. The quail were kept in pens (5 birds per pen). A total of 32 pens were randomly assigned to one of the four treatment groups as described in Table III.A.1. Prior to the initiation of treatment, one quail from each of the 32 pens was randomly chosen for hematology and serum chemistry analysis and removed from the pen, leaving 4 birds per pen for the treatment phase of the study. The data generated from the 32 pre-treatment quail provided reference intervals for the margin of safety study.

Table III.A.1 Treatment groups

Treatment	No. of Pens	No. of quail/pen*	Duration of treatment (days)
Control	8	5	63 to 67
100 ppm fenbendazole	8	5	63 to 67
200 ppm fenbendazole	8	5	63 to 67
300 ppm fenbendazole	8	5	63 to 67

*At study initiation, one quail from each pen was euthanized and blood samples were collected for hematology and serum chemistry analysis, leaving 4 birds per pen for the treatment phase of the study.

Drug Administration: Non-medicated basal diet was used as the control feed. The test article was mixed with the basal diet to prepare the Type C medicated feed containing 100, 200 and 300 ppm fenbendazole. The control and medicated feed were administered *ad libitum* for 63 to 67 consecutive days.

Measurements and Observations: General health observations of quail were conducted twice daily from arrival to the end of the study. The quail were initially weighed as a pen at the beginning of the study and were weighed individually at the end of the study. Feed consumption per pen was recorded for the entire study duration. Three quail from each pen were randomly selected at the end of the study for blood sampling and necropsy. After collecting blood samples for hematological and serum chemistry analysis, the selected quail were necropsied. All quail necropsied were examined grossly for lesions. Histopathologic examinations were performed on the quail from the control and the 300 ppm treatment groups.

Hematology and serum chemistry reference intervals for the interpretation of the clinical pathology results in the margin of safety study were generated from 32 randomly chosen quail prior to treatment initiation. The methodology used for the analysis of hematology and serum chemistry was the same for the margin of safety study and reference intervals.

Statistical Methods: Pen was the experimental unit. All fixed model effects were tested at a significance level of α = 0.10. Pairwise mean comparisons between each treatment group and the control group were performed using a significance level of α = 0.10. No adjustment was made for pairwise comparisons. Feed consumption was analyzed using repeated measures analysis of covariance (RMANCOVA) with treatment, time, and time by treatment as fixed effects and pre-treatment feed consumption as a covariate. Final body weight was analyzed using analysis of covariance (ANCOVA) with treatment as a fixed effect and beginning body weight as the covariate. Feed conversion and post-treatment clinical pathology were analyzed using analysis of variance (ANOVA) with treatment as a fixed effect. If there was significant difference among dose means, each of the dose group means were compared to the control group mean. Gross necropsy and histopathology observations were summarized by dose group.

Results: No treatment related effects were identified during the general health observations. Four birds died prior to scheduled euthanasia: one from the 100 ppm group, one from the 200 ppm group, and two from the 300 ppm group. All four birds underwent necropsy and histological evaluation; and the mortalities were determined to be unrelated to treatment. Body weight and feed efficiency were not significantly different between the treated and control groups. No significant differences were found for the hematology and serum chemistry parameters analyzed except for serum globulins, which were higher in one of the fenbendazole-treated groups (200 ppm) compared to the control group. The serum globulin values for the 200 ppm group were within the reference interval and the difference was not considered to be test article related. No treatment related effects were identified during gross necropsy, histopathology, and bone marrow smear evaluations.

Conclusions: Based upon the results of this study, fenbendazole is considered to be safe in quail when administered orally via medicated feed at 100 ppm for 21 consecutive days.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

The Agency evaluated the need to address the impact of the use of fenbendazole on antimicrobial resistance among bacteria of public health concern in or on fenbendazole-treated wild quail. After reviewing information (literature, data, etc.) both submitted by the sponsor and available in the public domain, the Agency determined:

- Fenbendazole is not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
- Fenbendazole is not used to treat gastroenteritis or other bacterial diseases in humans,
- Fenbendazole is not under development to treat a bacterial disease in humans, and
- Fenbendazole is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined that a microbial food safety assessment was not required for this approved use of fenbendazole in wild quail.

B. Toxicology

Reassessment of the codified Acceptable Daily Intake (ADI) or safe concentrations was not needed for this supplemental approval. The codified ADI for total residue of fenbendazole is 40 µg/kg of bodyweight *per* day, as listed under 21 CFR §556.275. The safe concentrations for total residues of fenbendazole in individual edible tissues are 4 ppm for muscle, 12 ppm for liver, 24 ppm for kidney, 24 ppm for fat or skin with fat, 0.64 ppm for milk, and 2.4 ppm for eggs. These values reflect the partition of the ADI between meat (50% of the ADI), milk (40% of the ADI), and eggs (10% of the ADI).

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      CVM did not require total residue and metabolism studies for this supplemental approval. The target tissue, marker residue, and tolerance assigned for fenbendazole residues in turkeys (a related major species) were applied to fenbendazole residues in quail (a minor species). The FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, contains a summary of the total residue and metabolism study for fenbendazole in turkeys.

   b. Comparative Metabolism Study

      CVM did not require comparative metabolism studies for this supplemental approval. Comparative metabolism of fenbendazole residues in quail (a minor species) and the toxicology model species is considered demonstrated by the comparative metabolism study in turkeys (a related major species). The FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, contains a summary of the comparative metabolism study for fenbendazole in turkeys.

   c. Study to Establish Withdrawal Period

      (1) Tissue Residue Depletion Study

      Title: Tissue Residue Depletion Study in Quail Administered Fenbendazole at 110 ppm in Medicated Feed for 21 days. (Study No. 353-HFS-2020)

      Study Dates: December 2020 to February 2022

      Study Locations: In-Life Facility: Lubbock, TX
      Analytical Laboratory (tissues): Amarillo, TX
      Analytical Laboratory (feed): Lawrence, KS

Test Material: Safe-Guard® (fenbendazole) 20% Type A medicated article

Study Design:

This study was conducted in compliance with Good Laboratory Practice (GLP) regulations. Adult Northern bobwhite quail, at least 16 weeks old weighing an average of 237.5 g on Study Day 0, were fed either the control diet or a diet containing 110 ppm fenbendazole *ad libitum* for 21 days. Six fenbendazole treated quail (3 males, 3 females) *per* time point were slaughtered at 0, 6, 24, 48, 72, and 96 hours withdrawal. Livers were collected from each animal and analyzed for fenbendazole sulfone using a validated analytical method.

Results: Concentrations of fenbendazole sulfone, the marker residue, were measured in liver (the target tissue). Results are summarized in Table IV.C.1 below. The 6-hour withdrawal time point was not included because the Quality Control (QC) samples failed during the analysis of those samples. The 72 and 96-hour withdrawal samples also were not included because those quail inadvertently received medicated feed during the withdrawal period. All samples analyzed at 48 hours withdrawal were below the Limit of Quantitation (LOQ) of 0.112 ppm.

Table IV.C.1. Mean Concentrations of Fenbendazole Sulfone (ppm ± standard deviation (S.D.)) in Quail Liver

Withdrawal Period (hours)	Fenbendazole Sulfone (ppm± S.D.)
0	1.857 ± 0.761
24	0.3599 ± 0.232

Because there were only two data points with values above the LOQ, a single timepoint upper tolerance limit (99th percentile of the population and the 95 percent confidence level) was calculated using the data at the 0-hour withdrawal time point. Using a k-factor of 5.065 (n = 6), an upper tolerance of 5.7 ppm was calculated which is below the 6 ppm tolerance. Therefore, the data support a 0-day withdrawal period.

2. Target Tissue and Marker Residue

   The target tissue and marker residue assigned for turkeys are applied to quail. Based on the information provided in the supplemental approval of NADA 131-675 dated July 3, 2000, for fenbendazole in turkeys, the target tissue is liver, and the marker residue is fenbendazole sulfone for fenbendazole in quail.

3. Tolerance

   The tolerance assigned for turkey liver is applied to quail. The tolerance for fenbendazole sulfone (the marker residue) in quail liver (the target tissue) is 6 ppm.

4. Withdrawal Period

   Based on a tolerance of 6 ppm, data from Study Number 353-HFS-2020 summarized above support assignment of a 0-day withdrawal period for the use of Safe-Guard® (fenbendazole) 20% Type A medicated article in quail when used according to label directions.

D. Analytical Method for Residues

1. Description of Analytical Method

   Five hundred milligrams of homogenized quail liver is fortified with the internal standard (fenbendazole sulfone-D_3) followed by the addition of 4 mL of methanol. The mixture is vortexed for 10 min. After centrifuge, the supernatant is decanted into a clean test tube. The tissue pellet is vortexed with another 4 mL aliquot of methanol. After centrifuge, the two supernatants are combined, and fresh methanol is added to make the volume of the extract up to 10 mL. An aliquot (50 µL) of the extract is diluted to 1 mL by the addition of 950 µL of an acetonitrile/water mixture, followed by liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis in the positive ion mode. The following transitions are monitored for quantitation:

   fenbendazole sulfone: m/z 332 → m/z 300
   fenbendazole sulfone-D_3: m/z 335 → m/z 300

   Sample extraction for the confirmatory procedure is identical to the one for the determinative procedure. Fenbendazole sulfone is detected by LC-MS/MS in the positive-ion mode. The following fenbendazole sulfone-specific ion transitions are monitored to obtain ion ratios, signal to noise ratios and retention time reproducibility data that meet the required acceptability criteria:

   m/z 332 → m/z 300
   m/z 332 → m/z 159
   m/z 332 → m/z 104

2. Availability of the Method

   The validated analytical method for analysis of residues of fenbendazole is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Safe-Guard® (fenbendazole) 20% Type A medicated article:

"WARNING: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. NOT FOR USE IN HUMANS. The Safety Data Sheet (SDS) contains more detailed occupational safety information. For customer service, adverse effects reporting, and/or a copy of the SDS, call 1-800-211-3573. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDAVETS, or http://www.fda.gov/reportanimalae."

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 Safe-Guard®, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above. Additionally, data demonstrate that residues in food products derived from species treated with Safe-Guard® will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed over the counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

This supplemental approval for Safe-Guard® (fenbendazole) 20% Type A medicated article qualifies for SEVEN years of exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the FD&C Act because it is a designated new animal drug under section 573(a) of the FD&C Act. Except as provided in section 573(c)(2) of the FD&C Act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as Safe-Guard® (fenbendazole) 20% Type A medicated article. Because the supplemental application included safety and effectiveness studies, this drug also qualifies for three years of exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act. This exclusivity begins as of the date of our approval letter and only applies to the indication For the treatment and control of *Aulonocephalus* spp. in wild quail. The exclusive marketing rights and applicable exclusivity run concurrently.

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval required 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.