Date of Approval: January 10, 2022

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

Cattle: Dairy and Beef Cattle;
Swine: Growing pigs, gilts, pregnant sows and boars;
and
Growing Turkeys

This supplement provides for 1) tolerances and tissue withdrawal periods in cattle, swine, and turkeys, and a milk discard time in cattle in accordance with a repartitioning of the acceptable daily intake (ADI); and 2) the addition of fourth stage larval indications for barberpole worms (*Haemonchus contortus & H. placei*), small stomach worms (*Trichostrongylus axei*), hookworms (*Bunostomum phlebotomum*), thread-necked intestinal worms (*Nematodirus helvetianus*), small intestinal worms (*Cooperia punctata & C. oncophora*), bankrupt worms (*Trichostrongylus colubriformis*), and nodular worms (*Oesophagostomum radiatum*) in cattle.

Sponsored by:

Intervet, Inc.

Executive Summary

This supplemental approval of Safe-Guard® (fenbendazole) 20% Type A medicated article (1) provides for tolerances and tissue withdrawal periods in cattle, swine, and turkeys, and a milk discard time in cattle in accordance with a repartitioning of the acceptable daily intake (ADI); and (2) adds fourth stage larval indications for certain gastrointestinal nematodes in cattle. 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.

Safe-Guard® 20% Type A medicated article is already approved for the treatment and control of the adult stage of lungworms, stomach worms, and/or intestinal worms in multiple species. The drug is now approved for the treatment and control of the fourth stage larvae of some of these parasites in cattle.

Proprietary Name	Established Name	Dosage Form	Application Type and Number	Sponsor
Safe-Guard®	fenbendazole	Type A medicated article	New Animal Drug Application (NADA) 131-675	Intervet, Inc.

Fenbendazole is a benzimidazole antiparasitic drug that is effective against a variety of nematode parasites. The drug disrupts energy metabolism in the parasites, essentially starving them by inhibiting glucose uptake, protein secretion, and microtubule production. The parasites' enzyme activity is also reduced.

FDA approved Safe-Guard® 20% Type A medicated article as an over-the-counter drug because the Agency determined that adequate "directions for use" can be written on the label in such a way that non-veterinarians can use the drug safely and effectively. The labeling for Safe-Guard® 20% Type A medicated article directs end-users to consult their veterinarian for help diagnosing, treating, and controlling parasite infections. In addition, the drug's labeling now includes information about antiparasitic resistance to help end-users better understand the proper use of antiparasitic drugs in general and ways to monitor and slow down the development of antiparasitic resistance at the farm level.

Safety and Effectiveness

The sponsor conducted a bridging study to compare the effectiveness of three oral formulations of Safe-Guard® in cattle with induced gastrointestinal nematode infections: Type C medicated feed made from Safe-Guard® 20% Type A medicated article, Safe-Guard® Suspension 10%, and Safe-Guard® Paste 10%. Safe-Guard® Suspension 10% is currently approved to treat fourth stage larval (L4) infections of certain gastrointestinal nematodes. The purpose of the study was to harmonize the L4 indications of the three formulations.

Holstein or Holstein cross steer calves were enrolled in the study and treated with levamisole phosphate during the acclimation period to eliminate pre-existing gastrointestinal parasites. The calves were assigned to one of three treatment groups (one group for each of the fenbendazole formulations) or to a control group. On Day -6, all calves were administered inoculum containing third stage larvae (L3) of several gastrointestinal nematodes that commonly infect cattle. The L3 are the infective stage of the parasites, and they molt to L4 and then into adult parasites inside the cattle.

On Day 0, (6 days after receiving the inoculum and when most of the L3 larvae would have molted to the L4 stage), the calves were treated with one of the three fenbendazole formulations at the same dose or given water at the same dose volume as Safe-Guard® Suspension 10% (control group). Three weeks later (between Days 21 and 23), the calves were necropsied and adult parasites were counted. Calves in the control group had adequate parasite infections, and compared to the control group, calves in each of the three treatment groups had significantly lower parasite counts. Safe-Guard® 20% Type A medicated article was greater than 99% effective against the representative parasites tested in the study. The study showed that Type C medicated feed manufactured from Safe-Guard® 20% Type A medicated article has similar effectiveness to Safe-Guard® Suspension 10% for treating and controlling L4 infections of certain gastrointestinal nematodes. Therefore, FDA determined that it is acceptable to harmonize the L4 indications for the two formulations. No adverse reactions were seen in the study.

The Freedom of Information (FOI) Summary for the original approval of Safe-Guard® Suspension 10%, dated September 2, 1983, contains a summary of target animal safety studies for cattle. The original approval of Safe-Guard® 20% Type A medicated article, published in the Federal Register (49 FR 3846) on January 31, 1984, contains a summary of target animal safety studies for swine. The FOI Summary for the supplemental approval of Safe-Guard® 20% Type A medicated article, dated July 3, 2000, contains a summary of target animal safety studies for growing turkeys.

Human Food Safety
Because fenbendazole products are approved for a variety of food-producing animals, including cattle, swine, and chickens, the use of the drug will result in residues in meat, milk, and eggs; therefore, the ADI is partitioned between these food commodities. When eggs were added as a commodity under an approval for another fenbendazole product, FDA revised the safe concentrations for all commodities based on the previously established ADI of 40 µg/kg body weight per day for total residues of fenbendazole (see the FOI Summary for Safe-Guard® AquaSol, dated October 2, 2015). As a result of these revised safe concentrations, FDA also reevaluated the tolerances, tissue withdrawal periods, and milk discard times for all fenbendazole products.

The revised tolerances for the target tissue, tissue withdrawal periods, and milk discard time (if applicable) for Safe-Guard® 20% Type A medicated article are listed below:

Species	Target Tissue	Marker Residue	Tolerance (parts per million, ppm)
Cattle	Liver	Parent fenbendazole	0.8
Cattle	Milk	Fenbendazole sulfoxide	0.22
Swine	Liver	Parent fenbendazole	3.2
Turkeys	Liver	Fenbendazole sulfone	6

Species	Tissue Withdrawal Period (days)	Milk Discard Time (hours)
Cattle	13	60
Swine	4	NA
Turkeys	0	NA

NA: Not applicable

The 4-day tissue withdrawal period in swine is supported by a new residue depletion study conducted for this supplemental approval based on the revised tolerance. FDA didn't require new residue depletion studies for cattle and turkeys because either the tolerance didn't change or studies conducted under previous approvals for Safe-Guard® products had sufficient data to determine the tissue withdrawal periods for both species and the milk discard time for cattle based on the revised tolerances.

Conclusions
Based on the data submitted by the sponsor for the approval of Safe-Guard® 20% Type A medicated article, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

NADA 131-675

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

Safe-Guard®

D. Drug Product Established Name

fenbendazole

E. Pharmacological Category

Antiparasitic

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[1]

200 g/kg (90.7 g/lb)

H. How Supplied

25 lb bag

I. Dispensing Status

Over-the-counter (OTC)

J. Dosage Regimen

Cattle/Dairy and Beef Cattle: 5 mg fenbendazole per kg body weight in a one (1) day treatment (2.27 mg fenbendazole per pound). Feed as the sole ration for one (1) day. Free-Choice Feeds: Type C free-choice medicated feed must be

[1] The sponsor of this individual currently marketed Type A medicated article may have approvals for other strengths that are for use in the same species and class, for the same indications, and at the same dosages, but are not currently marketing those strengths of this Type A medicated article. Such strengths, when legally marketed, are also approved for use in the manufacture of Type B and Type C medicated feeds that are the subject of this approval.

manufactured by a licensed feed mill according to an approved formula to provide a total of 5 mg per kg body weight fenbendazole over 3 to 6 days.

Swine/Growing pigs, gilts, pregnant sows and boars: 9 mg fenbendazole per kg body weight (4.08 mg fenbendazole per pound) to be fed as the sole ration over a period of 3 to 12 days.

Growing Turkeys: 14.5 g fenbendazole/ton of feed, to be fed as the sole ration for 6 days.

K. Route of Administration

Oral

L. Species/Class

Cattle/Dairy and Beef Cattle;
Swine/Growing pigs, gilts, pregnant sows and boars; and
Turkeys/Growing Turkeys

M. Indications

Cattle: Dairy and Beef Cattle

For the treatment and control of: **Lungworms**: Adult *Dictyocaulus viviparus;* **Stomach worms**: Adult brown stomach worms (*Ostertagia ostertagi*), Adult and fourth stage larvae barberpole worms (*Haemonchus contortus*), fourth stage larvae barberpole worms (*H. placei*), and Adult and fourth stage larvae small stomach worms (*Trichostrongylus axei*); **Intestinal worms** (Adult and fourth stage larvae): hookworms (*Bunostomum phlebotomum*), thread-necked intestinal worms (*Nematodirus helvetianus*), small intestinal worms (*Cooperia punctata & C. oncophora*), bankrupt worms (*Trichostrongylus colubriformis*), and nodular worms (*Oesophagostomum radiatum*).

Swine: Growing pigs, gilts, pregnant sows, and boars

For the treatment and control of: **Lungworms**: Adult *Metastrongylus apri*, adult *Metastrongylus pudendotectus*; **Gastrointestinal worms**: Adult and larvae (L3, L4 stages, liver, lung, intestinal forms) large roundworms (*Ascaris suum*), Adult nodular worms (*Oesophagostomum dentatum*, *O. quadrispinulatum*), Adult small stomach worms (*Hyostrongylus rubidus*), Adult and larvae (L2, L3, L4 stages-intestinal mucosal forms) whipworms (*Trichuris suis*); and **Kidney worms**: Adult and larvae *Stephanurus dentatus*.

Growing Turkeys

For the treatment and control of: **Gastrointestinal worms**: Roundworms, Adults and larvae (*Ascaridia dissimilis*); Cecal worms, Adults and larvae (*Heterakis gallinarum*), an important vector of *Histomonas meleagridis* (Blackhead).

N. Effect of Supplement

This supplement provides for 1) tolerances and tissue withdrawal periods in cattle, swine, and turkeys, and a milk discard time in cattle in accordance with a repartitioning of the acceptable daily intake (ADI); and 2) the addition of fourth stage larval indications for barberpole worms (*Haemonchus contortus & H. placei*), small stomach worms (*Trichostrongylus axei*), hookworms (*Bunostomum phlebotomum*), thread-necked intestinal worms (*Nematodirus helvetianus*), small intestinal worms (*Cooperia punctata* & *C. oncophora*), bankrupt worms (*Trichostrongylus colubriformis*), and nodular worms (*Oesophagostomum radiatum*) in cattle.

II. EFFECTIVENESS

A. Dosage Characterization

1. Cattle

   This supplemental approval does not change the previously approved dosage in cattle. The Freedom of Information (FOI) Summaries for the original approval of NADA 137-600 dated April 15, 1988, the supplemental approval of NADA 128-620 dated October 5, 1988, the supplemental approval of NADA 137-600 dated August 30, 1989, the supplemental approval of NADA 137-600 dated March 28, 1996, and the supplemental approval of NADA 131-675 dated September 5, 2008, contain dosage characterization information for dairy and beef cattle.

2. Swine

   This supplemental approval does not change the previously approved dosage in swine. The original approval of NADA 131-675 (49 FR 3846, dated January 31, 1984), and the FOI Summaries for the supplemental approval of NADA 131-675 dated November 22, 1988, and the supplemental approval of NADA 131-675 dated November 14, 1990, contain dosage characterization information for swine.

3. Growing Turkeys

   This supplemental approval does not change the previously approved dosage in growing turkeys. The FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, contains dosage characterization information for growing turkeys.

B. Substantial Evidence

1. CVM did not require effectiveness studies in swine or growing turkeys for this supplemental approval.

   The original approval of NADA 131-675 (49 FR 3846, dated January 31, 1984); and the FOI Summaries for the supplemental approval of NADA 131-675 dated November 22, 1988, and the supplemental approval of NADA 131-675 dated November 14, 1990, contain summaries of the studies that demonstrate

effectiveness of the drug for swine.

The FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, contains a summary of the studies that demonstrate effectiveness of the drug for growing turkeys.

2. Dose Confirmation Study in cattle

Title: A Bridging Study to Evaluate the Larvicidal Anthelmintic Efficacy of Various Formulations of Fenbendazole (FBZ) at a Dose Rate of 5.0 mg/kg bodyweight (BW) Orally, Under Controlled Conditions in Cattle with Experimentally-Induced Gastrointestinal Nematode Infections.
(Study No. 97-0020)

Study Dates: February 1998 to April 1998

Study Location: Knoxville, TN, United States

Study Design:

Objective: To compare the effectiveness of Type C medicated feed made from Safe-Guard® (fenbendazole) 20% Type A medicated article and Safe-Guard® (fenbendazole) Paste 10% with the effectiveness of Safe-Guard® (fenbendazole) Suspension 10% against artificially induced infections of fourth stage larvae of a representative abomasal nematode (*Trichostrongylus axei*) and representative intestinal nematode (*Cooperia punctata*), for the purpose of harmonizing the fourth stage larval indications of the three formulations.

Study Animals: 32 Holstein or Holstein cross steer calves, weighing 115 to 193 kg (253 to 425 lbs) on the day prior to treatment were enrolled in the study. Calves were treated with levamisole phosphate during acclimation to eliminate pre-existing gastrointestinal parasite infections.

Experimental Design: The study was conducted in accordance with FDA/CVM Guidelines on Good Target Animal Study Practices: Clinical Investigators and Monitors (1997). On Day -6, calves were inoculated orally with an inoculum that contained approximately 7,000 infective, third stage larvae (L3) of *Trichostrongylus axei* and approximately 20,000 L3 of *Cooperia* spp., as well as L3 of other common gastrointestinal nematodes of cattle. On Day -1, animals were ranked in descending order by body weight and randomly assigned to one of four treatment groups:

Table II.1. Treatment Groups

Group	Treatment Regimen	Number of Animals
1	Safe-Guard® Suspension 10% given orally at a dose of 5 mg fenbendazole/kg BW (2.3 mg/lb) which is equal to 2.3 mL/100 lbs	8
2	Type C medicated feed manufactured from Safe-Guard® 20% Type A medicated article given orally to each individual animal to ensure they received a dose of 5 mg fenbendazole/kg BW (2.3 mg/lb)	8
3	Safe-Guard® Paste 10% given orally at a dose of 5 mg fenbendazole/kg BW (2.3 mg/lb)	8
4	water (control) given orally at a dose of 2.3 mL/100 lbs	8

Drug Administration: On Day 0, (six days after L3 stage inoculation) cattle in Treatment Groups 1, 2, and 3 were treated orally with Safe-Guard® Suspension 10%, Type C medicated feed manufactured from Safe-Guard® 20% Type A medicated article, or Safe-Guard® Paste 10%, respectively. Cattle in Group 4 were treated with water using the same dose volume (2.3 mL per 100 lbs) as Safe-Guard® Suspension 10%.

Measurements and Observations: The study animals were necropsied between Day 21 and Day 23 following treatment for collection and counting of adult nematodes. General health observations were conducted at two, four, and 24 hours after drug administration and then daily for the remainder of the study.

Statistical Methods: The nematode counts of the treated and control groups were analyzed using analysis of variance. Mean contrasts were used to test for differences between pairs of treatments. All testing was two-sided at the significance level $\alpha=0.05$. Speciated parasite counts for each animal were transformed to the natural logarithm of (count + 1) for analysis and calculation of geometric means.

Results: Six out of eight control animals had adequate infections of *Trichostrongylus axei* (at least 200 adult worms) and all eight control animals had adequate infections of *Cooperia punctata* (at least 100 adult worms). For each of the three products and parasite species, there was a statistically significant ($p < 0.0001$) difference between the treated and control group nematode counts. Efficacy was calculated for each product separately using the formula: $[(C-T)/C] \times 100$, where C = geometric mean of worm counts for the control group and T = geometric mean of worm counts for the Safe-Guard® Suspension 10%, Type C medicated feed, or Safe-Guard® Paste 10% treatment groups.

Table II.2. Geometric mean worm counts and percent efficacy

Treatment	Number of Animals	Geometric Mean *T. axei* Worm Counts	Geometric Mean *C. punctata* Worm Counts	% Efficacy for *T. axei*	% Efficacy for *C. punctata*
Control (water)	8	196.65	1891.97	NA	NA
Safe-Guard® suspension 10%	8	0	1.14	100%	99.9%
Type C medicated feed manufactured from Safe-Guard® 20% Type A medicated article	8	0	1.33	100%	99.9%
Safe-Guard® paste 10%	8	0	0	100%	100%

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

Conclusions: This study demonstrates that Type C medicated feed made from Safe-Guard® (fenbendazole) 20% Type A medicated article and Safe-Guard® (fenbendazole) Paste 10% when dosed according to label directions (5 mg/kg BW) have comparable efficacy to Safe-Guard® (fenbendazole) Suspension 10% administered orally as a single dose of 5 mg/kg BW for the treatment and control of fourth stage larvae of *Trichostrongylus axei* and *Cooperia punctata*, which are representative abomasal and intestinal parasites, respectively. The demonstration of effectiveness against these two parasites provides the basis to grant the following fourth stage larval indications currently approved for Safe-Guard® (fenbendazole) Suspension 10% to all Type C medicated feeds for cattle made from Safe-Guard® (fenbendazole) 20% Type A medicated article: fourth stage larvae barberpole worms (*Haemonchus contortus & H. placei*), small stomach worms (*Trichostrongylus axei*), hookworms (*Bunostomum phlebotomum*), thread-necked intestinal worms (*Nematodirus helvetianus*), small intestinal worms (*Cooperia punctata & C. oncophora*), bankrupt worms (*Trichostrongylus colubriformis*), and nodular worms (*Oesophagostomum radiatum*).

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains a summary of target animal safety studies for dairy and beef cattle. The original approval of NADA 131-675 (49 FR 3846, dated January 31, 1984) contains a summary of target animal safety studies for swine. The FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, contains a summary of target animal safety studies for growing turkeys.

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 cattle, swine, and turkeys. After reviewing information (literature, data, etc.) currently 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 (or a similar class representative) is not under development to treat bacterial diseases in humans, and
- Fenbendazole is not indicated for a bacterial disease in a food-producing animal species.

Therefore, there was no need to develop or submit for review additional microbial food safety (antimicrobial resistance) information or data in support of the proposed use of fenbendazole in cattle, swine, and turkeys.

B. Toxicology

No additional toxicology information or data was required for this supplemental approval. The FOI Summaries for the original approval of NADA 128-620 dated September 2, 1983, the supplemental approval of NADA 137-600 dated March 28, 1996, the supplemental approval of NADA 131-675 dated February 10, 2000, and the original approval of NADA 141-449 dated October 2, 2015, contain summaries of all toxicology studies and information.

C. Establishment of the Final ADI

The final ADI is the toxicological ADI of 40 µg/kg BW/day for total residues of fenbendazole derived from a 6-month repeated dose oral toxicity study in dogs. The codified ADI is listed under 21 CFR §556.275.

D. Safe Concentrations for Total Residues in Edible Tissues

Because fenbendazole will result in residues in meat, milk and eggs, the available ADI of 40 ug/kg BW/day is partitioned between these edible tissues. As a result, the safe concentrations for total residues of fenbendazole in the 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).

E. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      Cattle

      No additional total residue and metabolism studies were required for this supplemental approval. The FOI Summaries for the original approval of NADA 128-620 dated September 2, 1983, and the supplemental approval of NADA 137-600 dated March 28, 1996, contain summaries of the total residue and metabolism studies.

      Swine

      No additional total residue and metabolism studies were required for this supplemental approval. The original approval of NADA 131-675 (49 FR 3846, dated January 31, 1984) contains a summary of the total residue and metabolism study in swine.

      Turkeys

      No additional total residue and metabolism studies were required for this supplemental approval. 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 in turkeys.

   b. Comparative Metabolism Study

      Cattle

      CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains summaries of the comparative metabolism studies for fenbendazole.

      Swine

      CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains summaries of the comparative metabolism studies for fenbendazole.

      Turkeys

      CVM did not require comparative metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains summaries of the comparative metabolism studies for fenbendazole.

c. Studies to Establish Withdrawal Period and/or Milk Discard Time

(1) Tissue Residue Depletion Study

Cattle

No additional residue depletion studies in cattle were required for this supplemental approval. The FOI Summary for the original approval of NADA 137-600 dated April 15, 1988, contains a summary of the residue depletion study in cattle.

Swine

Title: Residue Depletion Study of Fenbendazole in Pig Liver After Oral Administration of Safe-Guard 20% Type A Medicated Article (Study No. S17230-00)

Study Dates: April 2018 to November 2018

Study Locations: In-life Animal Phase: Tulare, CA, USA
Analytical Phase: Rahway, NJ, USA

Study Design:

Objective: The objective of this study was to determine the concentrations of fenbendazole in liver tissues from pigs after oral administration of Safe-Guard® (fenbendazole) 20% Type A medicated article at a target dose of 3.5 mg fenbendazole/kg BW/day in a Type C medicated feed for three consecutive days.

Study Animals: Forty-four crossbred pigs (22 barrows and 22 gilts) weighing 91.0 kg to 119.5 kg at Study Day -5 were used in this study.

Experimental Design: Two pigs were used to obtain control tissues. Six pigs (three females and three males) served as replacement animals. Pigs were randomly assigned to one of six treatment groups, such that each group contained three females and three males (three pigs *per* pen). Pigs in treatment groups were slaughtered at their assigned slaughter times (Table IV.1). The study was conducted in compliance with the Good Laboratory Practice (GLP) regulations (21 CFR Part 58).

Drug Administration: Pigs were treated with fenbendazole medicated feed at a target dose of 3.5 mg fenbendazole/kg BW/day for three consecutive days. Based on the actual medicated feed consumption *per* pen, the average consumed dose of fenbendazole over three days was 3.27-4.42 mg fenbendazole/kg BW/day (*i.e.,* a total of 9.8-13.3 mg fenbendazole/kg BW), which was greater than the currently approved dose of 9 mg fenbendazole/kg BW.

Table IV.1. Treatment groups and assigned slaughter times

Treatment Group	Number of Animals	Slaughter Time (Hours After Last Treatment)
1	3 males, 3 females	12
2	3 males, 3 females	18
3	3 males, 3 females	24
4	3 males, 3 females	30
5	3 males, 3 females	36
6	3 males, 3 females	42

Measurements: At the assigned withdrawal times (Table IV.1), pigs were slaughtered, and liver samples were collected. The liver samples were assayed for concentrations of fenbendazole by a validated liquid chromatography with mass spectrometric detection (LC-MS/MS) method. The method's limit of quantification (LOQ) was 0.729 ppm. Liver concentrations of fenbendazole less than the method LOQ were excluded from the analyses.

Statistical Method: The data were analyzed using a statistical algorithm that calculated the upper tolerance limit for liver fenbendazole concentrations for the 99th percentile with 95% confidence.

Results: Mean (± standard deviation) concentrations of fenbendazole in liver samples are presented in Table IV.2.

Table IV.2. Mean (± standard deviation) concentrations of fenbendazole in liver tissues from pigs treated with fenbendazole medicated feed for three consecutive days

Slaughter Time (Hours After Last Treatment)	Liver Fenbendazole Concentration (ppm)
12	3.96 ± 1.59
18	3.30 ± 1.18
24	4.03 ± 1.07
30	1.69 ± 0.65
36	2.17 ± 1.08*
42	1.40 ± 0.13

*Mean of four animals with fenbendazole concentrations above the LOQ
Mean of two animals with fenbendazole concentrations above the LOQ

The upper tolerance limit for liver fenbendazole concentrations for the 99th percentile with 95% confidence was less than the tolerance of 3.2 ppm in swine liver at 4 days after the last administration.

Turkeys

No additional residue depletion studies in turkeys were required for this supplemental approval. The FOI Summary for the supplemental

approval of NADA 131-675 dated July 3, 2000, contains a summary of the residue depletion study for turkeys.

(2) Milk Residue Depletion Study

Cattle

No additional milk residue depletion studies were required for this supplemental approval. The FOI Summary for the supplemental approval of NADA 137-600 dated March 28, 1996, contains a summary of the milk residue depletion study.

2. Target Tissue and Marker Residue

Cattle

Based on the results of the total residue and metabolism study provided in the FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, the target tissue is liver and the marker residue in tissues is parent fenbendazole (21 CFR §556.275).

Based on the results of the total residue and metabolism study provided in the FOI Summary for the supplemental approval of NADA 137-600 dated March 28, 1996, the marker residue in milk is fenbendazole sulfoxide (21 CFR §556.275).

Swine

Based on the results of the total residue and metabolism study provide in the original approval of NADA 131-675 (49 FR 3846, dated January 31, 1984), the target tissue is liver, and the marker residue is parent fenbendazole (21 CFR §556.275).

Turkeys

Based on the results of the total residue and metabolism study summarized in the FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, the target tissue is liver and the marker residue is fenbendazole sulfone (21 CFR §556.275).

3. Tolerances

Cattle

Liver: Based on a revised safe concentration of 12 ppm for liver listed in the FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, and total residue and metabolism study in cattle provided in the FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, the previously established tolerance of 0.8 ppm for parent fenbendazole in cattle liver is retained (21 CFR §556.275).

Milk: Based on a revised safe concentration of 0.64 ppm for milk listed in the FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, and total residue and metabolism study in cattle provided in the FOI Summary for the supplemental approval of NADA 137-600 dated March 28, 1996, a revised tolerance of 0.22 ppm is assigned as the tolerance for fenbendazole sulfoxide in milk.

Swine

A reassessment of the tolerance was not needed for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-449, dated February 11, 2016, contains summaries of the information used to establish the tolerance for fenbendazole in swine liver.

The tolerance for parent fenbendazole (marker residue) in swine liver (target tissue) is 3.2 ppm (21 CFR §556.275).

Turkeys

The residue and metabolism studies summarized in the FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, showed that total residues of fenbendazole were below the safe concentration of 12 ppm for liver at the 6-hour (*i.e.*, 0-day) withdrawal time point. The marker to total ratio at the 6-hour withdrawal time point was 59%, which results in a calculated revised tolerance of 7 ppm. The current tolerance of 6 ppm is lower and more conservative than 7 ppm. Therefore, the previously established tolerance of 6 ppm for fenbendazole sulfone in turkey liver is retained (21 CFR §556.275).

All species

The sponsor has fulfilled the requirements to establish a tolerance in the target tissue. The sponsor chose not to seek re-evaluation to establish a tolerance in muscle. Muscle is not the target tissue for any species listed above, and therefore the sponsor is not required to establish a tolerance in muscle. As a result, there is no longer a tolerance in muscle.

4. Withdrawal Periods and Milk Discard Time

Cattle

Tissues: The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains a summary of the residue chemistry studies to establish a withdrawal period in cattle tissues. Because the previously established tolerance in tissues has been preserved, the withdrawal period in cattle tissues remain unchanged. The withdrawal period for Safe-Guard® (fenbendazole) 20% Type A medicated article in cattle tissues is 13 days when used according to label directions.

Milk: The FOI summary for the supplemental approval of NADA 137-600 dated March 28, 1996, contains a summary of the residue chemistry studies to establish a milk discard time. Based on a revised tolerance of 0.22 ppm the

data support a revised milk discard time of 60 hours for use of Safe-Guard® (fenbendazole) 20% Type A medicated article when used according to label directions.

Swine

Based on a tolerance of 3.2 ppm, data from Study S17230-00 summarized above support assignment of a 4-day withdrawal period for the use of Safe-Guard® (fenbendazole) 20% Type A medicated article in swine when used according to label directions.

Turkeys

The residue data summarized in the FOI Summary for the supplemental approval of NADA 131-675 dated July 3, 2000, showed that total residues of fenbendazole in the edible tissues of turkeys are well below the safe concentrations for residues in turkeys at the 6-hour (*i.e.*, 0-day) withdrawal time point, and residues of fenbendazole sulfone in liver were below the tolerance. Thus, the withdrawal period for the use of Safe-Guard® (fenbendazole) 20% Type A medicated article in turkeys remains as zero when used according to label directions.

F. Analytical Method for Residues

1. Description of Analytical Method

   a. Determinative Procedures

      Cattle

      Liver: The determinative procedure for fenbendazole in bovine liver is based on extraction of fenbendazole from bovine liver and analysis of the extract by high pressure liquid chromatography with UV detection (HPLC-UV).

      Milk: Homogenized cattle raw milk is fortified with the deuterium-labeled internal standard (oxfendazole-d3) and extracted twice with methanol. After centrifugation, an aliquot of the methanol extract is diluted with water and analyzed using LC-MS/MS with positive ion multiple reaction monitoring (MRM). Ion transitions m/z 316 → m/z 159 for oxfendazole and m/z 319 → m/z 159 for oxfendazole-d3 are monitored for quantitation.

      Swine

      After adding the deuterium-labeled fenbendazole internal standard (FBZ-d3) to homogenized swine liver, the sample is extracted twice with methanol by shaking on a vortex mixer. After centrifugation, the supernatant is diluted with methanol and analyzed using LC-MS/MS. Quantitation is based on ion transition of m/z 300 → m/z 268 for fenbendazole and m/z 303 → m/z 268 for FBZ-d3.

Turkeys

After adding the deuterium-labeled internal standard (FBZ-sulfone-d3) to homogenized turkey liver tissue, the sample is extracted twice with methanol by shaking on a vortex mixer. After centrifugation, the supernatant is diluted with methanol and analyzed using liquid chromatography with mass spectrometric detection (LC-MS/MS). Quantitation is based on ion transitions of m/z 332 → m/z 300 for fenbendazole-sulfone and m/z 335 → m/z 300 for fenbendazole-sulfone-d3.

b. Confirmatory Procedure

Cattle

Liver: For the confirmation of fenbendazole, the bovine liver extract is analyzed by thin-layer chromatography, followed by conversion of the isolated fenbendazole to the benzyl derivative and analysis of the benzyl derivative by HPLC-UV.

Milk: Sample extraction for the confirmatory procedure is identical to the one for the determinative procedure. Fenbendazole sulfoxide (oxfendazole) is detected using a tandem mass analyzer (MS/MS). Oxfendazole-specific ion transitions (m/z 316 → m/z 159, m/z 316 → m/z 191, and m/z 316 → m/z 284) are monitored for the confirmatory procedure.

Swine

Sample extraction for the confirmatory procedure is identical to the one for the determinative procedure. Fenbendazole is detected using a tandem mass spectrometer (MS/MS). Fenbendazole-specific ion transitions (m/z 300 → m/z 268, m/z 300 → m/z 159 and m/z 300 → m/z 131) are monitored to obtain ion ratios, signal to noise ratios, and retention times that meet the required acceptability criteria.

Turkeys

Sample extraction for the confirmatory procedure is identical to the one for the determinative procedure. Fenbendazole sulfone is detected using a tandem mass analyzer (MS/MS). Three fenbendazole sulfone-specific ions (m/z 332 → m/z 300, m/z 332 → m/z 159 and m/z 332 → m/z 104) are monitored to obtain ion ratios, signal to noise ratios, and retention times that meet the required acceptability criteria.

2. Availability of the Method

The validated analytical methods for analysis of residues of fenbendazole are 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® 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 and 21 CFR part 514. The data demonstrate that Safe-Guard®, when used according to the label, is safe and effective for the additional indications for treatment and control of various fourth stage larvae of gastrointestinal nematodes in cattle. Additionally, data demonstrate that residues in food products derived from species treated with Safe-Guard® 20% Type A medicated article 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® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental application included an effectiveness study. This exclusivity begins as of the date of our approval letter and only applies to the fourth stage larval indications for cattle that are approved in the supplemental application.

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

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