Date of Approval: March 24, 2021

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 132-872

Safe-Guard®

(fenbendazole)

Paste

Cattle: Beef and Dairy Cattle

This supplement provides for 1) tolerances, a tissue withdrawal period, and a milk discard time 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* and *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*).

Sponsored by:

Intervet, Inc.

Executive Summary

This supplemental approval of Safe-Guard® (fenbendazole) Paste 10% (1) provides for tolerances, a tissue withdrawal period, and a milk discard time in accordance with a repartitioning of the acceptable daily intake (ADI); and (2) adds fourth stage larval indications for certain gastrointestinal nematodes in cattle. Safe-Guard® Paste 10% is already approved for the treatment and control of the adult stage of lungworms, stomach worms, and intestinal worms in beef and dairy cattle. The drug is now approved for the treatment and control of the fourth stage larvae of some of these parasites.

Proprietary Name	Established Name	Dosage Form	Application Type and Number	Sponsor
Safe-Guard®	fenbendazole	Paste	New Animal Drug Application (NADA) 132-872	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® Paste 10% 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® Paste 10% directs end-users to consult their veterinarian for help diagnosing, treating, and controlling parasite infections in cattle. 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%. 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® Paste 10% was greater than 99% effective against the representative parasites tested in the study. The study showed that Safe-Guard® Paste 10% 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.

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 NADA 141-449 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.

For Safe-Guard® Paste 10%, the target tissue is liver, and the tolerance for parent fenbendazole, the marker residue in cattle liver, is 0.8 ppm. In milk, the marker residue is fenbendazole sulfoxide and its tolerance in milk is 0.22 ppm. The withdrawal period for tissues is 8 days, and the milk discard time is 96 hours.

Conclusions
Based on the data submitted by the sponsor for the approval of Safe-Guard® Paste 10%, 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 132-872

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

Paste

G. Amount of Active Ingredient

10% (100 mg/g)

H. How Supplied

92 g syringe and 290 g tube

I. Dispensing Status

Over-the-counter (OTC)

J. Dosage Regimen

Single dose of 2.3 mg/lb (5 mg/kg) body weight (BW)

K. Route of Administration

Oral

L. Species / Class

Cattle/Beef and Dairy Cattle

M. Indication

For the treatment and control **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*)

N. Effect of Supplement

This supplement provides for 1) tolerances, a tissue withdrawal period, and a milk discard time in accordance with a repartitioning of the ADI; and 2) the addition of fourth stage larval indications for barberpole worms (*Haemonchus contortus* and *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*).

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The FOI Summary for the original approval of NADA 132-872 dated February 29, 1984; the supplemental approval of NADA 128-620 dated October 5, 1988; and the supplemental approval of NADA 132-872 dated March 28, 1996; contain dosage characterization information for beef and dairy cattle.

B. Substantial Evidence

1. Dose Confirmation Study

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 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 α=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] x 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 *Trichostrongylus axei* Worm Counts	Geometric Mean *C. punctata* Worm Counts	% Efficacy for *Trichostrongylus 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 Safe-Guard® (fenbendazole) Paste 10%: fourth stage larvae barberpole worms (*Haemonchus contortus* and *H. placei*), small stomach worms

(*Trichostrongylus axei*), hookworms (*Bunostomum phlebotomum*), thread-necked intestinal worms (*Nematodirus helvetianus*), small intestinal worms (*Cooperia punctata* and *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 beef and dairy cattle.

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

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 132-872 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

      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 132-872 dated March 28, 1996, contain summaries of the total residue and metabolism studies in cattle.

   b. Comparative Metabolism Study

      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. Study to Establish Withdrawal Period and/or Milk Discard Time

      (1) Tissue Residue Depletion Study

         No additional residue depletion studies in cattle were required for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains a summary of the residue depletion study in cattle.

      (2) Milk Residue Depletion Study

         No additional milk residue depletion studies were required for this supplemental approval. The FOI Summary for the supplemental approval of NADA 132-872, dated March 28, 1996, contains a summary of the milk residue depletion study.

2. Target Tissue and Marker Residue

   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 liver 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 132-872 dated March 28, 1996, the marker residue in milk is fenbendazole sulfoxide (21 CFR §556.275).

3. Tolerances

   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 the 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 the total residue and metabolism study in cattle provided in the FOI Summary for the supplemental approval for NADA 132-872 dated March 28, 1996, a revised tolerance of 0.22 ppm is assigned as the tolerance for fenbendazole sulfoxide in milk.

   Muscle: 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 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 Period and Milk Discard Time

   Tissues: The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains summaries of the residue chemistry studies to establish a withdrawal period in cattle tissues. Because the previously established tolerance in tissues has been retained, the withdrawal period in cattle tissues remain unchanged. The withdrawal period for Safe-Guard® Paste 10% in cattle tissues is 8 days when used according to label directions.

   Milk: The FOI Summary for the supplemental approval of NADA 132-872 dated March 28, 1996, contains summaries of the residue chemistry studies to establish a milk discard time. Based on a revised tolerance of 0.22 ppm for fenbendazole sulfoxide in milk, the data support a milk discard time of 96 hours for use of Safe-Guard® (fenbendazole) Paste 10% when used according to label directions.

F. Analytical Method for Residues

1. Description of Analytical Method

   a. Determinative Procedure

      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.

b. Confirmatory Procedure

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.

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® Paste 10%:

WARNING: NOT FOR USE IN HUMANS. KEEP OUT OF REACH OF CHILDREN. 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® Paste 10%, when used according to the label, is safe and effective for the 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® Paste 10% 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® Paste 10% 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 fourth stage larval indications 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.