Date of Approval: June 14, 2021

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 128-620

Safe-Guard®

Panacur®

fenbendazole

Suspension

Cattle: Beef and Dairy Cattle

Goats

This supplement provides for tolerances, a tissue withdrawal period, and a milk discard time in cattle; and a tolerance and tissue withdrawal period in goats in accordance with a repartitioning of the acceptable daily intake (ADI).

Sponsored by:

Intervet, Inc.

Executive Summary

This supplemental approval of Safe-Guard® (fenbendazole) Suspension 10% and Panacur® (fenbendazole) Suspension 10% provides for tolerances, a tissue withdrawal period, and a milk discard time in cattle; and a tolerance and tissue withdrawal period in goats in accordance with a repartitioning of the acceptable daily intake (ADI).

Proprietary Names	Established Name	Dosage Form	Application Type and Number	Sponsor
Safe-Guard® Panacur®	fenbendazole	Suspension	New Animal Drug Application (NADA) 128-620	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.

Safe-Guard® Suspension 10% is approved as an over-the-counter drug for beef and dairy cattle and goats at a dose of 2.3 mg/lb (5 mg/kg) body weight (BW). Panacur® Suspension 10% is approved as a prescription drug for beef and dairy cattle at a dose of 2.3 mg/lb (5 mg/kg) BW and for beef cattle at a dose of 4.6 mg/lb (10 mg/kg) BW. As an OTC product, the labeling for Safe-Guard® Suspension 10% directs end-users to consult their veterinarian for help diagnosing, treating, and controlling parasite infections. In addition, the labeling for both Safe-Guard® Suspension 10% and Panacur® Suspension 10% 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 Freedom of Information (FOI) Summaries for the original approval of Safe-Guard® Suspension 10% under NADA 128-620, dated September 2, 1983, the supplemental approval of NADA 128-620, dated October 5, 1988, and the supplemental approval of NADA 128-620, dated March 28, 1996, contain summaries of studies that demonstrate the effectiveness of the drug for cattle.

The FOI Summary for the original approval of Safe-Guard® Suspension 10% under NADA 128-620, dated September 2, 1983, contains a summary of target animal safety studies for cattle.

Public Master File 5118 contains a summary of studies that demonstrate target animal safety and effectiveness of the drug for goats.

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 BW 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.

In cattle and goats, the target tissue is liver, and the tolerance for parent fenbendazole, the marker residue in liver, is 0.8 parts per million (ppm). In milk (dairy cattle), the marker residue is fenbendazole sulfoxide and its tolerance in milk is 0.22 ppm.

In beef and dairy cattle, the tissue withdrawal period is 8 days. In dairy cattle, the milk discard time is 48 hours. Panacur® Suspension 10% is only approved at the 5 mg/kg BW dose for dairy cattle. A tissue withdrawal period was not established in pre-ruminating calves; therefore, Safe-Guard® Suspension 10% and Panacur® Suspension 10% are not approved for beef calves less than 2 months of age, dairy calves, or veal calves.

In goats, the tissue withdrawal period is 6 days. A milk discard time was not established; therefore, Safe-Guard® Suspension 10% is not approved for lactating goats.

Conclusions

Based on the data submitted by the sponsor for the approval of Safe-Guard® Suspension 10% and Panacur® Suspension 10%, FDA determined that the drugs are safe and effective when used according to their labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 128-620

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Names

Safe-Guard®

Panacur®

D. Drug Product Established Name

fenbendazole

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Suspension

G. Amount of Active Ingredient

100 mg/mL (10%)

H. How Supplied

Safe-Guard®: 125 mL, 1000 mL, 1 Gallon, and 10 L bottles

Panacur®: 1000 mL and 1 Gallon bottles

I. Dispensing Status

Safe-Guard®: Over-the-counter (OTC)

Panacur®: Prescription (Rx)

J. Dosage Regimen

Safe-Guard®:

Beef and Dairy Cattle: Single dose of 2.3 mg/lb (5 mg/kg) body weight (BW)

Goats: Single dose of 2.3 mg/lb (5 mg/kg) BW

Panacur®:

Beef and Dairy Cattle: Single dose of 2.3 mg/lb (5 mg/kg) BW

Beef Cattle: Single dose of 4.6 mg/lb (10 mg/kg) BW

K. Route of Administration

Oral

L. Species/Class

Safe-Guard®: Cattle/Beef and Dairy Cattle; and Goats

Panacur®: Cattle/Beef and Dairy Cattle

M. Indications

Beef and Dairy Cattle (Safe-Guard® and Panacur®): 2.3 mg/lb (5 mg/kg) BW 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 & 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*).

Beef Cattle Only (Panacur®): 4.6 mg/lb (10 mg/kg) BW for the treatment and control of: **Stomach worms** (4th stage inhibited larvae): *Ostertagia ostertagi* (Type II Ostertagiasis); **Tapeworms**: *Moniezia benedeni*.

Goats (Safe-Guard®): 2.3 mg/lb (5 mg/kg) BW for the treatment and control of: **Stomach worms** (adults): *Haemonchus contortus* and *Teladorsagia circumcincta.*

N. Effect of Supplement

This supplement provides for tolerances, a tissue withdrawal period, and a milk discard time in cattle; and a tolerance and tissue withdrawal period in goats in accordance with a repartitioning of the acceptable daily intake (ADI).

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage for beef and dairy cattle. The FOI Summaries for the original approval of NADA 128-620 dated September 2, 1983, the supplemental approval of NADA 128-620 dated October 5, 1988, and the supplemental approval of NADA 128-620 dated March 28, 1996, contain dosage characterization information for beef and dairy cattle.

This supplemental approval does not change the previously approved dosage for goats. Public Master File 5118 contains dosage characterization information for goats.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summaries for the original approval of NADA 128-620 dated September 2, 1983, the supplemental approval of NADA 128-620 dated October 5, 1988, and the supplemental approval of NADA 128-620 dated March 28, 1996, contain summaries of studies that demonstrate effectiveness of the drug for beef and dairy cattle. Public Master File 5118, as referenced in the FOI Summary for the supplemental approval of NADA 128-620 dated April 25, 1994, contains a summary of studies that demonstrate effectiveness of the drug for goats.

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. Public Master File 5118, as referenced in the FOI Summary for the supplemental approval of NADA 128-620 dated April 25, 1994, contains a summary of the target animal safety study that demonstrates safety of the drug for goats.

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 and goats. 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 and goats.

B. Toxicology

No additional toxicology information or data were 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 128-620 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 128-620 dated March 28, 1996, contain summaries of the total residue and metabolism studies.

   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 Milk Discard Time

      (1) Tissue Residue Depletion Study

         <u>Cattle</u>

         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.

         <u>Goats</u>

         No additional tissue residue depletion studies were required for this

supplemental approval. Public Master File 5118, as referenced in the FOI Summary for the supplemental approval of NADA 128-620 dated April 25, 1994, contains a summary of the residue depletion study in goats.

(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 128-620 dated March 28, 1996, contains a summary of the milk residue depletion study in cattle.

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 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 128-620 dated March 28, 1996, the marker residue in milk is fenbendazole sulfoxide (21 CFR §556.275).

Goats

Based on the information provided in the FOI Summary for the supplemental approval of NADA 128-620 dated April 25, 1994, the target tissue is liver and the marker residue is parent fenbendazole (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 128-620, dated March 28, 1996, a revised tolerance of 0.22 ppm is assigned as the tolerance for fenbendazole sulfoxide in milk.

Goats

The tolerance assigned for cattle liver is applied to goats. The previously established tolerance of 0.8 ppm for parent fenbendazole in cattle liver is retained, therefore the previously established tolerance of 0.8 ppm for parent fenbendazole in goat liver is retained (21 CFR §556.275).

Cattle and Goats

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 for either cattle or goats.

4. Withdrawal Period 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 retained, the withdrawal period in cattle tissues remain unchanged. The withdrawal period for Safe-Guard® Suspension 10% and Panacur® Suspension 10% in cattle tissues is 8 days when used according to label directions.

Milk: The FOI Summary for the supplemental approval of NADA 128-620 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 for fenbendazole sulfoxide in milk, the data support a revised milk discard time of 48 hours for use of Safe-Guard® Suspension 10% when used according to label directions.

Goats

Public Master File 5118, as referenced in the FOI Summary for the supplemental approval of NADA 128-620 dated April 25, 1994, contains a summary of the residue depletion study in goats. Because the previously established tolerance in tissues has been preserved, the withdrawal period in goat tissues remain unchanged. The withdrawal period for Safe-Guard® Suspension 10% in goat tissues is 6 days when used according to label directions.

F. Analytical Method for Residues

1. Description of Analytical Method

a. Determinative Procedures

Cattle and Goat Liver: The determinative procedure for fenbendazole in bovine or goat liver is based on extraction of fenbendazole from bovine or

goat liver and analysis of the extract by high pressure liquid chromatography with UV detection (HPLC-UV).

Cattle 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 Procedures

Cattle and Goat Liver: For the confirmation of fenbendazole, the bovine or goat 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.

Cattle 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® and Panacur®:

WARNINGS: 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 and 21 CFR part 514. The data demonstrate that Safe-Guard® Suspension 10% and Panacur® Suspension 10%, when used according to the label, are safe and effective for the indications listed in Section I.M. above. Additionally, data demonstrate that residues in food products

derived from species treated with Safe-Guard® Suspension 10% and Panacur® Suspension 10% will not represent a public health concern when the product is used according to the label.

A. Marketing Status

Safe-Guard® Suspension 10% 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.

Panacur® Suspension 10%, 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 for the diagnosis and treatment of the parasites that require the use of the higher dose (10 mg/kg) for beef cattle.

B. Exclusivity

Safe-Guard® Suspension 10% and Panacur® Suspension 10%, as approved in our approval letter do not qualify for marketing exclusivity under section 512(c)(2)(F) of the Federal Food, Drug, and Cosmetic Act.

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.