

Date of Approval: January 5, 2018

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-449

SafeGuard® AquaSol

Fenbendazole oral suspension

Broiler chickens, replacement chickens, breeding chickens, and
laying hens

For the treatment and control of adult *Ascaridia galli* in broiler chickens and replacement chickens and for the treatment and control of adult *A. galli* and *Heterakis gallinarum* in breeding chickens and laying hens.

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-449

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

SafeGuard® AquaSol

D. Product Established Name

Fenbendazole oral suspension

E. Pharmacological Category

Anthelmintic

F. Dosage Form

Suspension

G. Amount of Active Ingredient

200 mg/mL

H. How Supplied

1 L and 3785 mL (1 gallon) high density polyethylene plastic containers

I. Dispensing Status

OTC

J. Dosage Regimen

Daily dose of 1.0 mg/kg BW (0.454 mg/lb) for 5 consecutive days

K. Route of Administration

Oral in drinking water

L. Species/Class

Broiler chickens, replacement chickens, breeding chickens, and laying hens

M. Indication

For the treatment and control of adult *Ascaridia galli* in broiler chickens and replacement chickens and for the treatment and control of adult *A. galli* and *Heterakis gallinarum* in breeding chickens **and laying hens**.

N. Effect of Supplement

This supplement provides for the following: 1) the addition of "and laying hens" to the indication for treatment and control of adult *A. galli* and *H. gallinarum*; 2) the removal of the limitation of "intended to become breeding chickens" from "replacement chickens" in the treatment and control portion of the *A. galli* only part of the indication; and 3) the removal of the limitation, "Not for use in laying hens and replacement chickens intended to become laying hens" in the indication.

II. EFFECTIVENESS**A. Dosage Characterization**

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-449 dated October 2, 2015, contains dosage characterization information for species, dosage, and other applicable information.

B. Substantial Evidence

The FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, contains a summary of the dose confirmation and field effectiveness studies that were conducted to evaluate the effectiveness of SafeGuard® AquaSol against adult *A. galli* in broiler chickens and replacement chickens and against adult *A. galli* and *H. gallinarum* in breeding chickens and laying hens. A combination of studies in different classes of chickens was used in the determination of effectiveness against the parasite species and classes of chickens listed above.

III. TARGET ANIMAL SAFETY

The FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, contains a summary of the target animal safety studies that were conducted to evaluate the safety of SafeGuard® AquaSol in broiler chickens, replacement chickens, breeding chickens, and laying hens. A combination of studies in different classes of chickens was used in this determination of safety within the classes of chickens listed above.

IV. HUMAN FOOD SAFETY**A. Antimicrobial Resistance**

CVM did not require additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, contains a summary of all information used to assess the risk to microbial food safety (antimicrobial resistance).

B. Impact of Residues on Human Intestinal Flora

CVM did not require additional information for the impact of residues on human intestinal flora for this supplemental approval. The FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, contains a summary of all information used to assess the impact of fenbendazole residues on human intestinal flora.

C. Toxicology

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this supplemental approval. The FOI Summaries for the original approval of NADA 128-620, dated August 22, 1983, NADA 132-872, dated March 28, 1996, NADA 131-675, dated February 10, 2000, and NADA 141-449, dated October 2, 2015, contain a summary of all toxicology studies and information.

D. Establishment of the Final ADI

The final ADI is the toxicology 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.

E. Safe Concentrations for Total Residues (edible tissues)

The safe concentrations for total residues of fenbendazole in the individual edible tissues of chickens are 4 ppm for muscle, 12 ppm for liver, 24 ppm for skin with fat in natural proportions, and 2.4 ppm for eggs. These values reflect the partition of the ADI between meat, milk, and eggs (50% of the ADI for meat, 40% of the ADI for milk, and 10% of the ADI for eggs).

F. Residue Chemistry

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Studies

- (1) **Title:** A target animal metabolism study in eggs of laying hen following repeated oral administration of 1.5 mg [¹⁴C]-fenbendazole per kg body weight to laying hen. Study Number V-0079-3632

Study Director: Agnes Toutin

Study Dates: October 25, 2010 to February 1, 2011

Study Facility: Avogadro, Fontenilles, France

Study Facility, metabolite characterization: INRA, Toulouse, France

The study was conducted according to Good Laboratory Practices, with the exception of HPLC characterization component.

Test Material: The ¹⁴C-fenbendazole used in the study was radiolabeled at the 2-position of the benzimidazole heterocycle, which is the same site of radiolabeling as with the tracer used in the earlier total residue

studies in other species. The specific activity of the test material was 0.194 mCi/mg, with a radiopurity of greater than 98%.

Test Animals: Fifteen Pondeuse noire laying hens were used. Their age was approximately 6 months old at the first treatment, with a mean weight the day before treatment of 1.63 kg.

Dosing: Birds were dosed orally by gavage, divided into three doses which were administered approximately 3 hours apart. The total daily dose was 1.5 mg fenbendazole/kg BW. Birds were dosed for five consecutive days.

Sample Collection: Eggs were collected from Study Day 2 to Study Day 13. The white and yolk were homogenized as one sample.

Analysis: Total radioactive residues in eggs were measured by combustion and liquid scintillation counting. For metabolite profiling, pooled egg samples were extracted using acetonitrile and analyzed using HPLC-MS/MS in MRM mode. For cold marker residue determination, egg samples were analyzed using a HPLC method with fluorescence detection following a liquid extraction and oxidation and solid phase extraction on cartridges.

Results: Extraction recovery from pooled eggs ranged from 87.2 to 96.1%. For metabolic profiling, three metabolites were observed: oxfendazole, fenbendazole sulfone, and fenbendazole. Fenbendazole sulfone was the predominant metabolite, comprising 53.73 to 91.41% of total radioactive residues; with oxfendazole residues comprising 2.27 to 36.32% of total radioactive residues. Fenbendazole was only observed at Day 7 (Day 2 withdrawal), and comprised 6.38% of total radioactive residues. The results from this study demonstrate that the most appropriate marker residue for fenbendazole in eggs is fenbendazole sulfone.

- (2) **Title:** A total residue depletion study in chicken eggs following oral administration of 1.5 mg [^{14}C]-fenbendazole per kg body weight to laying hens on 12 consecutive days. Study Number S12173-00-DWF-MET-PO.

Study Director: Agnes Toutin

Study Dates: January 23, 2013 to May 13, 2013

Study Facility: Avogadro, Fontenilles, France

A statement was provided stating the study was conducted in accordance with OECD Principles of Good Laboratory Practice (GLP) and FDA GLP.

Test Material: The ^{14}C -fenbendazole used in the study was radiolabeled at the 2-position of the benzimidazole heterocycle. The specific activity of the undiluted test material was 189.4 μCi , with a radiopurity of 98.1%.

Dosing Formulation: The test item was formulated as 20% fenbendazole suspension in water, also containing 10% polysorbate 80, 0.5% simethicone emulsion, and 2% benzyl alcohol.

Test Animals: Lochmann Selected Leghorn hens, 39 weeks of age at treatment, were used.

Dosing: Hens received 20% fenbendazole suspension *via* gavage at a dose of 1.5 mg fenbendazole/kg BW daily for 12 consecutive days. The total daily doses of 1.5 mg fenbendazole/kg BW were split into 3 individual doses.

Analysis: Eggs from treated birds laid on Study Days 11 to 15 were collected for fenbendazole analysis. Total radioactive residues in eggs were measured by combustion and liquid scintillation counting. Fenbendazole sulfone (the marker residue) was measured using a validated HPLC-MS/MS method.

Results: Mean total (TRR) and marker (FBZ sulfone) concentrations in eggs are presented in IV.F. 1 (a) 2 below.

Table IV.F. 1 (a) 2. Mean residue concentrations in eggs after administration of 1.5 mg [¹⁴C]-fenbendazole /kg body weight/day for 12 days (n= 8 animals).

<u>Study Day</u> <u>(withdrawal day)</u>	<u>TRR (ppm eq.)</u>	<u>FBZ sulfone (ppm)</u>
Day 11 (-1)	0.734	0.550
Day 12 (0)	0.724	0.569
Day 13 (1)	0.708	0.585
Day 14 (2)	0.566	0.497
Day 15 (3)	0.444	0.383

The marker to total ratio at zero-day withdrawal (Day 12) is 0.78, which results in a tolerance of 1.8 ppm (safe concentration in eggs of 2.4 ppm * 0.78 = 1.87 rounded down to 1.8 ppm).

b. Comparative Metabolism Study

CVM did not require a comparative metabolism study for this approval. Results from the comparative metabolism studies for fenbendazole have been summarized in the original approval of NADA 128-620 dated August 22, 1983.

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

CVM did not require a tissue residue depletion study for this approval. The data in study #S12173-00-DWF-MET-PO show that total residues of fenbendazole in eggs of treated chickens at zero-day withdrawal are well below the safe concentration of 2.4 ppm for residues in eggs.

2. Target Tissue and Marker Residue

The data in study #V-0079-3632 show that the predominant residue present in eggs is fenbendazole sulfone. Therefore, the marker residue for residues of fenbendazole in eggs is fenbendazole sulfone.

3. Tolerance

The tolerance for fenbendazole sulfone (the marker residue) in eggs is 1.8 ppm.

4. Withdrawal Period and Milk Discard Time

The results of study #S12173-00-DWF-MET-PO demonstrate that total residues in eggs are below the safe concentration at zero-day withdrawal. Therefore, the withdrawal period is zero.

G. Analytical Method for Residues

1. Determinative Procedure

The deuterium-labeled internal standard (FBZ-sulfone-d3) is added to homogenized chicken egg and the sample is extracted twice with methanol. After centrifuging the mixture, the supernatant is diluted with methanol and analyzed using liquid chromatography with mass spectrometric detection (LC-MS/MS). Quantitation is based on the m/z 300 ion from FBZ-sulfone and FBZ-sulfone-d3.

2. Confirmatory Procedure

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

3. Availability of the Methods

The methods are available from the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY

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

"User Safety Warnings: Not for use in humans. Keep out of reach of children. Protective gloves should be used and care should be taken when handling the product to avoid skin and eye exposure and accidental ingestion. Accidental exposure may result in skin and eye irritation. Accidental ingestion may cause gastrointestinal disturbances and hypersensitivity reactions in humans. 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-FDA-VETS, or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>."

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 SafeGuard® AquaSol, when used according to the label, is safe and effective for the treatment and control of adult *Ascaridia galli* in broiler chickens and replacement chickens and for the treatment and control of adult *A. galli* and *Heterakis gallinarum* in breeding chickens and laying hens. Additionally, data demonstrate that residues in food products derived from species treated with SafeGuard® AquaSol 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

The supplemental approval for SafeGuard® AquaSol, qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application contained effectiveness and target animal safety studies (conducted at the time of the original approval dated October 2, 2015). This exclusivity begins as of the date of our approval letter and only applies to laying hens and replacement chickens intended to become laying hens.

C. Supplemental Applications

This supplemental NADA did not require 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 Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.