Date of Approval: March 17, 2008

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 131-675

SAFE-GUARD

Fenbendazole
20% Type A Medicated Article
Dairy and Beef Cattle

Free-choice liquid Type C medicated feed for use in dairy and beef cattle.

Sponsored by:

Intervet Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 131-675
B. Sponsor:	Intervet Inc. P.O. Box 318 29160 Intervet Lane Millsboro, DE 19966 Drug Labeler Code: 057926
C. Proprietary Name:	SAFE-GUARD
D. Established Name:	Fenbendazole
E. Pharmacological Category:	Anthelmintic
F. Dosage Form:	Type A medicated article
G. Amount of Active Ingredient:	200 grams per kilogram (90.7 grams per pound)
H. How Supplied:	25 lb (11.34 kg) bag
I. How Dispensed:	OTC
J. Dosage:	5 mg fenbendazole/kg body weight in a one day treatment or in free-choice Type C medicated feeds fed for 3 to 6 days
K. Route of Administration:	Oral, via feed
L. Species/Classes:	Dairy and Beef Cattle
M. Indications:	For the removal and control of: **Lungworms: (***Dictyocaulus viviparus).* **Stomach worms:** Barberpole worms (*Haemonchus contortus*), brown stomach worms (*Ostertagia ostertagi*), small stomach worms (*Trichostrongylus axei*). **Intestinal worms:** Hookworms (*Bunostomum phlebotomum*), thread-necked intestinal worms (*Nematodirus helvetianus*), small intestinal worms (*Cooperia punctata* and *C. oncophora*). **Bankrupt worms** (*Trichostrongylus colubriformis*). **Nodular worms** (*Oesophagostomum radiatum).*

N. Effect of Supplement: This supplement provides for the Type A medicated article to be used to manufacture a free-choice liquid Type C medicated feed for use in dairy and beef cattle.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summaries for the original approval of SAFE-GUARD (fenbendazole) 20% Type A medicated article as a complete Type C medicated feed or a Type C medicated feed top dress (NADA 137-600) dated April 15, 1988, and the supplemental approval of SAFE-GUARD (fenbendazole) Type A medicated article as a free-choice Type C medicated feed vitamin/mineral supplement fed over 3 to 6 days dated August 30, 1989, contain dosage characterization information for cattle at the 5 mg/kg body weight dose with one day administration and over a three to six day feeding interval.

B. Substantial Evidence:

The previous approval for the fenbendazole free-choice Type C medicated feed vitamin/mineral supplement fed for 3 to 6 days did not contain data for effectiveness against lungworms (*Dictyocaulus viviparus*). Since this parasite is not in the gastrointestinal tract and must be exposed to the drug by means of the bloodstream, effectiveness studies were conducted. The remainder of the parasites on the fenbendazole free-choice Type C medicated feed vitamin/mineral supplement label were granted for the fenbendazole liquid Type C medicated feed without further effectiveness testing as the dose and dose interval remain the same and both formulations are Type C medicated feeds. Two studies were conducted to evaluate the effectiveness of fenbendazole liquid Type C medicated feed for the removal and control of lungworms *(Dictyocaulus viviparus).* Each study satisfied the following criteria to demonstrate substantial evidence of effectiveness for the lungworm indication:

1. Adequacy of infection was demonstrated by the presence of $\geq$ 10 adult lungworms in the respiratory tract.

2. There was a significant treatment effect between medicated and non-medicated groups (at the two-sided $\alpha = 0.05$ significance level).

3. The percent efficacy was equal to or greater than 90%.

The individual studies are summarized below.

1. Dose Confirmation Study

a. Title: "A controlled effectiveness study of a free choice Fenbendazole medicated Type C for the removal and control of lungworm (*Dictyocaulus viviparus*) infections in cattle." (Study No. 2606-002-01)

b. Investigator: Craig R. Reinemeyer, DVM, PhD, East Tennessee Clinical Research, Rockwood, TN

c. Study Design:

1) *Objective:* The objective of the study was to determine that the effectiveness of fenbendazole liquid Type C medicated feed is adequate to remove and control *D. viviparus* induced infections when a total of 5 mg of fenbendazole/kg of body weight in the fenbendazole liquid Type C medicated feed is dosed over a 6 day interval.

2) *Study Animals:* Twenty ruminating Holstein or Holstein cross bull calves and steers, 2 to 5 months of age at the time of inoculation, and weighing between 64.5 kg and 197.0 kg the day prior to treatment initiation (Day -1) were included in the study. After inoculation calves were eligible for enrollment if they had evidence of lungworm infection based on the examination of feces using the Baermann technique. Two additional (sentinel) calves were necropsied on Day -5 to confirm adequate infection.

3) *Treatment groups:* Study animals were randomly assigned to one of two treatment groups: fenbendazole liquid Type C medicated feed (10 animals), or non-medicated Type C liquid feed (10 animals).

4) *Housing:* Animals were housed in individual pens from one to a few days prior to treatment through the time of necropsy (Day 16).

5) *Infection: D. viviparus* larvae (L_1) were collected from three donor calves with natural patent infections and matured to infective stage larvae (L_3) for inoculation. Each animal was inoculated *per os* with 750 infective stage *D. viviparus* larvae (L_3) on Day -42 and Day -41.

6) *Drug Administration*: The test article was fenbendazole liquid Type C medicated feed formulated to 504 grams fenbendazole per ton (0.71897 mg fenbendazole per mL). The total dose of 5 mg fenbendazole per kg body weight was given as equal divided doses across 6 consecutive days ($1/6^{th}$ of the total dose per day) orally via rumen intubation. Calves in the control group were given non-medicated Type C liquid feed in equal divided doses across 6 consecutive days at a dose volume equivalent to the fenbendazole dose.

7) *Test Duration:* All cattle were necropsied 16 days post-treatment.

8) *Measurements and Observations:* Lungworms obtained from each animal at necropsy were counted and identified.

9) *Statistical Analysis:* Parasite counts for each animal were transformed to the natural logarithm of (count + 1) and were fit to a mixed model for analysis and calculation of geometric means. The treated and control groups were compared using a two–sided test at significance level α=0.05. Efficacy was calculated as 100[(C-T)/C], where T and C are the geometric means of worm counts for the treated and control groups, respectively.

d. Results:

Table 1: Therapeutic efficacy of fenbendazole liquid Type C medicated feed against lungworms

Number of adequately infected control animals	Geometric Mean (Controls)	Geometric Mean (Fenbendazole Type C Liquid feed)	Percent Efficacy	Probability
7	22.1	0.0	100%	<0.001

e. Adverse Reactions: There were no adverse reactions to fenbendazole liquid Type C medicated feed reported in this study.

2. Dose Confirmation Study

a. Title: "A controlled effectiveness study of a free choice Fenbendazole medicated Type C for the removal and control of lungworm (*Dictyocaulus viviparus*) infections in cattle." (Study No. 2606-002-02)

b. Investigator: Larry L. Smith, R&D Inc., Readstown, WI

c. Study Design:

1) *Objective:* The objective of the study was to determine that the effectiveness of a fenbendazole liquid Type C medicated feed is adequate to remove and control *D. viviparus* induced infections when a total of 5 mg of fenbendazole/kg of body weight in the fenbendazole liquid Type C medicated feed is dosed over a 6 day interval.

2) *Study Animals:* Twenty ruminating Holstein bull calves and steers, 3 to 5 months of age at the time of inoculation, and weighing between 130.6 kg and 190.2 kg the day prior to treatment initiation (Day -1) were included in the study. After inoculation calves were eligible for enrollment if they had

evidence of lungworm infection based on the examination of feces using the Baermann technique. Two additional (sentinel) calves were necropsied on Day -6 to confirm adequate infection.

3) *Treatment groups:* Study animals were randomly assigned to one of two treatment groups: fenbendazole liquid Type C medicated feed (10 animals), or non-medicated Type C liquid feed (10 animals).

4) *Housing:* Animals were housed in individual pens from one to a few days prior to treatment through the time of necropsy (Day 16).

5) *Infection: D. viviparus* larvae (L_1) were collected from three donor calves with natural patent infections and matured to infective stage larvae (L_3) for inoculation. Each animal was inoculated *per os* with 1,000 infective stage *D. viviparus* larvae (L_3) on Day -35 and Day -34.

6) *Drug Administration:* The test article was fenbendazole liquid Type C medicated feed formulated to 504 grams fenbendazole per ton (0.71897 mg fenbendazole per mL). The total dose of 5 mg fenbendazole per kg body weight was given as equal divided doses across 6 consecutive days ($1/6^{th}$ of the total dose per day) orally via rumen intubation. Calves in the control group were given non-medicated Type C liquid feed in equal divided doses across 6 consecutive days at a dose volume equivalent to the fenbendazole dose.

7) *Test Duration:* All cattle were necropsied 16 days post-treatment.

8) *Measurements and Observations:* Lungworms obtained from each animal at necropsy were counted and identified.

9) *Statistical Analysis:* Parasite counts for each animal were transformed to the natural logarithm of (count + 1) and were fit to a mixed model for analysis and calculation of geometric means. The treated and control groups were compared using a two-sided test at significance level $\alpha=0.05$. Efficacy was calculated as 100[(C-T)/C], where T and C are the geometric means of worm counts for the treated and control groups, respectively.

d. Results:

Table 2: Therapeutic efficacy of fenbendazole liquid Type C medicated feed against lungworms

Number of adequately infected control animals	Geometric Mean (Controls)	Geometric Mean (Fenbendazole Type C Liquid feed)	Percent Efficacy	Probability
10	109.9	0.43	99.6%	<0.001

e. Adverse Reactions: There were no adverse reactions to fenbendazole liquid Type C medicated feed reported in this study.

Overall Conclusions of the Dose Confirmation Studies: Fenbendazole liquid Type C medicated feed is effective against lungworms (*D. viviparus*) when fed free-choice over a 3 to 6 day period.

Three well-controlled clinical studies at representative geographic locations across the U.S. were conducted with fenbendazole liquid Type C medicated feed formulated to contain 504 g of fenbendazole per ton to demonstrate consumption of the drug within 3 to 6 days when offered to dairy and beef cattle on pasture on a free-choice basis.

3. Consumption Study

a. Title: "Determination of the Consumption Rate of a Free Choice Fenbendazole Medicated Type C Liquid Feed by Pasture Cattle" (Study # 2606-001-01).

b. Investigator: Stacey A. Gunter, Ph.D., Southwest Research and Extension Center, Hope, AR

c. Study Design:

1) *Objective:* The study was conducted to demonstrate that consumption of a fenbendazole liquid Type C medicated feed offered to cattle on pasture on a free-choice basis will provide the approved total dose of 5 mg fenbendazole/kg body weight over a 3 to 6 day consumption period.

2) *Study Animals:* Forty-five cross-bred beef steers, approximately 15 months of age, and weighing between 574 and 928 pounds at processing were used in the study.

3) *Treatment groups:* Fifteen animals were randomly assigned to each of three replicate pastures. All calves received non-medicated Type C liquid feed

during acclimation followed by the fenbendazole liquid Type C medicated feed during the treatment phase.

4) *Housing:* All animals were housed on pasture during the study.

5) *Drug Administration:* Animals in each pasture were given free-choice access to a lick tank feeder containing either the non-medicated (12-day acclimation period) or fenbendazole liquid Type C medicated feed (treatment period) containing 504 g of fenbendazole per ton.

6) *Measurements and Observations:* The amount of liquid feed consumed was measured daily. The measurements continued on a daily basis until the total dose of 5 mg fenbendazole/kg body weight had been consumed by a pasture replicate.

d. Results:

The animals consumed sufficient fenbendazole liquid Type C medicated feed to provide a total dose of 5 mg fenbendazole/kg of body weight in an average of 3 days.

Table 3. Summary of days needed to consume the fenbendazole liquid Type C medicated feed

	Pasture Number			Site Summary†	
	1	2	3	Mean	Std. Dev.
Days	4	3	2	3.0	1.0

†Sample mean and standard deviation across pastures.

e. Conclusion: The fenbendazole liquid Type C medicated feed formulation used in this study was a suitable method of administering the total dose of 5 mg fenbendazole/kg of body weight on a free choice basis to grazing cattle over a 3 to 6 day feeding period.

f. Adverse Reactions: There were no adverse reactions to fenbendazole liquid Type C medicated feed reported in this study.

4. Consumption Study

a. Title: "Determination of the Consumption Rate of a Free Choice Fenbendazole Medicated Type C Liquid Feed by Pasture Cattle" (Study # 2606-001-02).

b. Investigator: Mary I. Wray, PhD, Intervet Inc. Research Farm, De Soto, KS

c. Study Design:

1) *Objective*: The study was conducted to demonstrate that consumption of a fenbendazole liquid Type C medicated feed offered to cattle on pasture on a free-choice basis will provide the approved total dose of 5 mg fenbendazole/kg body weight over a 3 to 6 day consumption period.

2) *Study Animals*: Forty-five cross-bred beef heifers, 14 to 18 months of age, and weighing between 588 and 760 pounds at processing were used in the study.

3) *Treatment groups*: Fifteen animals were randomly assigned to each of three replicate pastures. All calves received non-medicated Type C liquid feed during acclimation followed by the fenbendazole liquid Type C medicated feed during the treatment phase.

4) *Housing*: All animals were housed on pasture during the study.

5) *Drug Administration:* Animals in each pasture were given free-choice access to a lick tank feeder containing either the non-medicated (8-day acclimation period) or fenbendazole liquid Type C medicated feed (treatment period) containing 504 g of fenbendazole per ton.

6) *Measurements and Observations*: The amount of liquid feed consumed was measured daily. The measurements continued on a daily basis until the total dose of 5 mg fenbendazole/kg body weight had been consumed by a pasture replicate.

g. Results:

The animals consumed sufficient fenbendazole liquid Type C medicated feed to provide a total dose of 5 mg fenbendazole/kg of body weight in an average of 4 days.

Table 4. Summary of days needed to consume the fenbendazole liquid Type C medicated feed

	Pasture Number			Site Summary†	
	1	2	3	Mean	Std. Dev.
Days††	--	4	4	4.0	0

†Sample mean and standard deviation across pastures.
††The measurement of medicated feed for pasture 1 stopped after Day 1.

h. Conclusion: The fenbendazole liquid Type C medicated feed formulation used in this study was a suitable method of administering the total dose of 5 mg fenbendazole/kg of body weight on a free choice basis to grazing cattle over a 3 to 6 day feeding period.

i. Adverse Reactions: There were no adverse reactions to fenbendazole liquid Type C medicated feed reported in this study.

5. Consumption Study

a. Title: "Determination of the Consumption Rate of a Free Choice Fenbendazole Medicated Type C Liquid Feed by Pasture Cattle" (Study # 2606-001-04).

b. Investigator: Terry N. TerHune, D.V.M., HMS Veterinary Development, Inc., Tulare, CA

c. Study Design:

1) *Objective:* The study was conducted to demonstrate that consumption of a fenbendazole liquid Type C medicated feed offered to cattle on pasture on a free-choice basis will provide the approved total dose of 5 mg fenbendazole/kg body weight over a 3 to 6 day consumption period.

2) *Study Animals*: Forty-five cross-bred beef steers, approximately 7 months of age, and weighing between 472 and 620 pounds at processing were used in the study.

3) *Treatment groups*: Fifteen animals were randomly assigned to each of three replicate pastures. All calves received non-medicated Type C liquid feed during acclimation followed by the fenbendazole liquid Type C medicated feed during the treatment phase.

4) *Housing*: All animals were housed on pasture during the study.

5) *Drug Administration*: Animals in each pasture were given free-choice access to a lick tank feeder containing either the non-medicated (14-day acclimation period) or fenbendazole liquid Type C medicated feed (treatment period) containing 504 g of fenbendazole per ton.

6) *Measurements and Observations*: The amount of liquid feed consumed was measured daily. The measurements continued on a daily basis until the total dose of 5 mg fenbendazole/kg body weight had been consumed by a pasture replicate.

j. Results:

The animals consumed sufficient fenbendazole liquid Type C medicated feed to provide a total dose of 5 mg fenbendazole/kg of body weight in an average of 5 days.

Table 5. Summary of days needed to consume the fenbendazole liquid Type C medicated feed

	Pasture Number			Site Summary†	
	1	2	3	Mean	Std. Dev.
Days	5	5	5	5.0	0

†Sample mean and standard deviation across pastures.

k. Conclusion: The fenbendazole liquid Type C medicated feed formulation used in this study was a suitable method of administering the total dose of 5 mg fenbendazole/kg of body weight on a free choice basis to grazing cattle over a 3 to 6 day feeding period.

l. Adverse Reactions: There were no adverse reactions to fenbendazole liquid Type C medicated feed reported in this study.

Overall Consumption Study Statistical Analysis:

The average number of days to consume fenbendazole liquid Type C medicated feed averaged across the 3 sites was 4 days (see the following table).

Table 6. Summary of days needed to consume the fenbendazole liquid Type C medicated feed across sites

Number of pastures†	Mean	Standard deviation
8	4.0	1.07

†Only 2 pastures were included for the Kansas site.

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 fenbendazole in cattle.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains a summary of all toxicology studies. An acceptable daily intake (ADI) of 40 micrograms per kilogram of body weight per day has been previously codified for total residues of fenbendazole (21 CFR 556.275).

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983,

contains a summary of the total residue and metabolism study in cattle. The FOI Summary for the original approval of NADA 137-600 dated April 15, 1988, contains the tissue residue depletion study in cattle.

The FOI Summary for the supplemental approval under NADA 132-872 dated March 28, 1996, contains a summary of the total residue and metabolism study in milk, establishes the safe concentration for total residues of fenbendazole in milk, and assigns the tolerance for residues of fenbendazole sulfoxide, the marker residue in milk. The FOI Summary for the supplemental approval of NADA 137-600 dated March 28, 1996, contains a summary of the milk residue depletion study in lactating dairy cattle. The FOI Summary for the supplemental approval of NADA 128-620 dated May 9, 2000, provides for the application of new consumption values of tissues, the recalculation of safe concentrations for total residues of fenbendazole, and the assignment of a tolerance for residues of parent fenbendazole in muscle.

C. Microbial Food Safety:

Fenbendazole is not an antimicrobial product so Microbial Food Safety did not have to be addressed.

D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 128-620 dated September 2, 1983, contains the analytical method summary for fenbendazole in cattle tissue. The FOI Summary for the supplemental approval of NADA 137-600 dated March 28, 1996, contains the analytical method summary for fenbendazole in milk.

V. USER SAFETY:

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

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN. NOT FOR USE IN HUMANS. The Material Data Safety Sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS, or for assistance contact customer service at 1-800-441-8272.

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 (fenbendazole) 20% Type A medicated article, when used according to the label, is safe and effective for the removal and control of lungworm and various gastrointestinal parasites. Additionally, data demonstrate that residues in food products

derived from dairy and beef cattle treated with SAFE-GUARD (fenbendazole) 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:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity apply only to the use of fenbendazole liquid Type C medicated feed for the removal and control of lungworms (*Dictyocaulus viviparus*), one of the parasite species for which this supplement is approved.

C. Supplemental Applications:

In accordance with the Center's supplemental approval policy 21 CFR 514.106(b)(2), this is a Category II change which did not require a reevaluation of safety and effectiveness data in the parent application.

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:
SAFE-GUARD (fenbendazole) 20% Type A medicated article
Fenbendazole Free-Choice Liquid Type C medicated feed