I. GENERAL INFORMATION

NADA Number:	137-600
Sponsor:	Hoechst Roussel Vet 30 Independence Boulevard P.O. Box 4915 Warren, New Jersey 08876-1258
Established Name:	fenbendazole
Trade Names:	Safe-Guard® 20% Type A Medicated Article Safe-Guard® 0.5% Cattle Top Dress Safe-Guard® 35% Free Choice Mineral
Dosage Form:	Type A medicated article Type B & C medicated feeds
Marketing Status:	over-the-counter
Pharmacological Category:	antiparasitic
Effect of Supplement:	This supplement provides for the use of Safe-Guard® premixes for the removal and control of gastrointestinal parasites and lungworm in a new class, dairy cattle of breeding age.

II. INDICATIONS FOR USE AND LABEL DOSE

Cattle, including dairy cattle of breeding age

5 mg/kg dose for the removal and control of:

- Lungworm: *Dictyocaulus viviparus*
- Stomach Worms:

  Ostertagia ostertagi (brown stomach worm)
  Haemonchus contortus/placei (barberpole worm)
  Trichostrongylus axei (small stomach worm)

- Intestinal Worms:

  Bunostomum phlebotomum (hookworm)
  Nematodirus helvetianus (threadnecked intestinal worm)
  Cooperia oncophora, Cooperia punctata (small intestinal worms)
  Trichostrongylus colubriformis (bankrupt worm)
  Oesophagostomum radiatum (nodular worm)

III. EFFECTIVENESS

Efficacy was established in the original approval under NADA 137-600 and its supplements (49 FR 3846; January 31, 1984; as amended 51 FR 7397; March 3, 1986; 53 FR 14788; April 26, 1988; 53 FR 48533; December 1, 1988; 54 FR 36963; September 6; 1989; 55 FR 48231; November 20, 1990; 57 FR 34516; August 5, 1992). No new studies were conducted to establish effectiveness for the use of fenbendazole in dairy cattle of breeding age.

IV. TARGET ANIMAL SAFETY

Animal safety was established in the original approval under NADA 137-600 and its supplements (49 FR 3846; January 31, 1984; as amended 51 FR 7397; March 3, 1986; 53 FR 14788; April 26, 1988; 53 FR 48533; December 1, 1988; 54 FR 36963; September 6; 1989; 55 FR 48231; November 20, 1990; 57 FR 34516; August 5, 1992). No new studies were conducted to establish animal safety for the use of fenbendazole in dairy cattle of breeding age.

V. HUMAN FOOD SAFETY

A. Toxicity Tests:

Toxicity and teratogenicity studies conducted at Hoechst Research Laboratories in Frankfurt, Germany, and in the United States were summarized in the FOI Summary for the original approval of fenbendazole in a food-producing species under NADA 128-620 (48 FR 42809; Sept. 20, 1983).

B. Previously Established Safe Concentrations and Tolerances:

The safe concentrations established for total residues of fenbendazole in edible tissues of cattle are 5 ppm in muscle, 10 ppm in liver, 15 ppm in kidney , and 20 ppm in fat. A tolerance of 0.8 ppm parent fenbendazole (the marker residue) in cattle liver (the target tissue) was established with the original approval under NADA 128-620.

Under a supplement to NADA 132-872 (61 FR 29477; June 11, 1996), a safe concentration for total residues of fenbendazole in milk of 1.67 ppm (1/3 of the 5 ppm safe concentration in muscle tissue) was established. Two pivotal, milk residue depletion studies using radiolabeled fenbendazole suspension were summarized in the FOI summary for the supplemental approval of Safe-Guard® Suspension 10% in lactating dairy cows under NADA 128-620 (61 FR 29477; June 11, 1996).

A third pivotal milk residue depletion “cold” study using nonradiolabeled fenbendazole in the intended market formulations was conducted at LSU at the same time.

C. Milk Residue Tolerance Study: LAV # 1591 SVM (Nov. 3, 1992 to July 16, 1993)

This study was conducted to determine the total quantity of fenbendazole and its metabolites in whole milk as a function of time and to expand the examination to include use of the actual market formulation. An additional objective was to ascertain activity of fenbendazole residues and its metabolites in three commonly used milk antibiotic screening tests: the Charm II assay, the Delvotest P, and the *Bacillus stearothermophilis* disc assay (BSDA).

Study Director:	Dr. Steven A. Barker, School of Veterinary Medicine, Louisiana State University
Test Article Administration:	fenbendazole Safe -Guard® 0.5% Cattle Top Dress Pellets administered at 5 mg/kg as a single dose via feed
Study Animals:	11 lactating Holstein cows, average 545 kg body weight, milking ≥20 kg/day

The ten treatment cows received fenbendazole as Safe-Guard® 0.5% Cattle Top Dress Pellets in an amount to equal 5.0 mg fenbendazole/kg body weight at a dose of 5.0 mg fenbendazole/kg body weight. The control cow was untreated.

Cows were machine milked in the morning prior to treatment. Milk samples collected at that milking were used as blank controls for the study. Serial milk samples (100 mL) were taken at the 4:00 AM and 4:00 PM milkings for seven days following fenbendazole treatment.

For metabolic profiling, milk samples were extracted by matrix solid phase dispersion (MSPD) technique. The amount of parent drug and metabolites was determined quantitatively by HPLC analysis using UV diode array detection. The identity of peaks was matched with known standards for the metabolites of fenbendazole based on retention time and UV-diode array spectra.

The administration of fenbendazole at a target dose of 5.0 mg/kg body to lactating dairy cattle produced residues in whole milk identifiable as fenbendazole sulfoxide, fenbendazole sulfone and trace quantities of fenbendazole. Peak residue time in milk was 24 hours after administration, and the peak fenbendazole sulfoxide marker level was 0.18 ± 0.10 mcg/mL (Table 5.1). No fenbendazole residues were detected in the control cow.

Table 5.1. Mean concentrations (+/-sd) of fenbendazole and marker metabolites in whole milk as a function of time following oral administration of FBZ, fed as Safe-Guard® Cattle Top Dress pellets at a rate of 5.0 mg fenbendazole/kg body weight to ten lactating dairy cows**.**

time (hours) after fenbendazole dosing	fenbendazole (mcg/mL)	FBZ sulfoxide (mcg/mL)	FBZ sulfone (mcg/mL)
0	nd*	0.00 (0.00)	0.00 (0.00)
12	nd	0.13 (0.06)	0.00 (0.00)
24	nd	0.18 (0.10)	0.05 (0.02)
36	nd	0.13 (0.08)	0.07 (0.04)
48	nd	0.05 (0.05)	0.06 (0.04)
60	nd	0.01 (0.02)	0.04 (0.04)
72	nd	0.00 (0.00)	0.01 (0.01)

*No residues detected. No residues were detected in milk from the control cow.
**Marker Residue

Antibiotic residue test screening was conducted on milk samples from three (3) treated cows chosen randomly. The samples were collected at 12-hour intervals for 72 hours post-dose. Tests performed included the Charm II assay, Delvotest P, and BSDA. Zero time samples were included in all antibiotic screening tests; Delvotest P and BSDA also included milk collected from the control animal at 12-hour intervals for 72 hours post-dose. Examinations indicated that the incurred residues from treated cows had no discernible or consistent effect on the assays. No sample from any cow examined gave a positive response to the Delvotest P and BSDA. Assay results of ten antibiotic classes indicated that fenbendazole and its metabolites do not interfere or cross-react with any consistency in the Charm II assay.

It was concluded that the fenbendazole sulfoxide marker residue level was below the tolerance level; therefore, total residues were below the established safe concentration for milk. A zero-day withdrawal period was approved for use of fenbendazole in feed at 5 mg/kg body weight in dairy cattle of breeding age. It was further concluded that use of fenbendazole does not interfere with routine antibiotic drug screening.

F. Milk Discard and Slaughter Withdrawal Time:

The milk residue depletion studies described in Subsection C, above, demonstrates that the maximum levels of fenbendazole residues in milk are well below the 1.67 ppm safe concentration and 0.6 ppm tolerance when lactating dairy cattle are treated at the approved dosing rate of 5 mg/kg body weight. Accordingly, a zero-day withdrawal period was approved for use of fenbendazole (Safe-Guard® 20% Type A Medicated Article, Safe-Guard® 0.5% Cattle Top Dress, Safe-Guard® 35% Free Choice Mineral), at 5 mg fenbendazole/kg, in dairy cattle of breeding age (61 FR 29478, June 11, 1996).

The 13-day preslaughter withdrawal time established in the original approval of NADA 137-600 (53 FR 14788; April 26, 1988) as codified in 21 CFR 558.258 applies to lactating dairy cows treated with fenbendazole in this manner.

G. Regulatory Methods:

A regulatory milk assay method is not required because of the establishment of a zero milk withdrawal period in lactating dairy cattle. However, an HPLC assay method is on file at FDA/CVM in Rockville, MD. A regulatory tissue method was developed as part of the original fenbendazole approval. The method, entitled, "Determination Procedure for the Measurement of Fenbendazole in Bovine Liver Tissue", is on file at the FDA's Freedom of Information Office, 5600 Fishers Lane, Rockville**,** MD 20857.

VI. AGENCY CONCLUSIONS

The data submitted in support of these supplemental applications satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and implementing regulations at Part 514 of Title 21 of the Code of Federal Regulations (21 CFR 514). The data demonstrate that fenbendazole Type A medicated article, and Type B and Type C medicated feeds, when administered as a single dose of 5 mg/kg to cattle, including dairy cattle of breeding age, are safe and effective for the treatment of internal parasitism due to common species of lungworm, stomach worms, and intestinal worms.

The toxicology data on fenbendazole submitted with the original application to NADA 128-620 (48 FR 42809; Sept. 20, 1983) allowed the establishment of a safe concentration of 1.67 ppm for total residues of fenbendazole in milk. From the residue and metabolite data submitted with this supplemental application, a tolerance of 0.6 ppm is established as the tolerance for residues in milk of the fenbendazole metabolite fenbendazole sulfoxide (the marker residue). Because the maximum levels of residues found in milk of fenbendazole-treated cattle are well below the safe concentration and tolerance noted above, no discard of milk (zero milk withdrawal) is required. The preslaughter withdrawal time of 13 days established for treated dairy cattle is the same as that established for cattle under the original NADA 137-600.

In accordance with 21 CFR 514.106(b)(2), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Adequate directions for use of the product to treat lactating dairy cows have been written for the layman, and the conditions for use are likely to be followed in practice. Therefore, the Center for Veterinary Medicine has concluded that these products (Safe-Guard® 20% Type A Medicated Article, Safe-Guard® 0.5% Cattle Top Dress, and Safe-Guard® 35% Free Choice Mineral) shall continue to have over-the-counter (OTC) status.

The agency has determined under 21 CFR 25.33(a) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. The Agency's finding of no significant impact (FONSI) and the evidence supporting this finding are on public display in the Dockets Management Branch (HFA-305), Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, Maryland 20852.

VII. APPROVED PRODUCT LABELING (Attached)

Facsimile bag label - Safe-Guard ® 20% Type A Medicated Article
Facsimile bag label - Safe-Guard ® 0.5% Top Dress
Facsimile package and box label - Safe-Guard ® 35% Free-Choice Mineral
Specimen Blue Bird, label Type B medicated feed
Specimen Blue Bird, label Type C medicated feed

cc:
Courtesy copy for the sponsor
HFV-199/NADA 137-600 (original)
HFV-2 (Mailing list)
HFV-15 (FOI staff)
HFV-102 (GADQC Reserve Copy)
HFV-102 Green Book (NTurner)
HFA-305(Dockets Management Branch)
HFR-MA350 (NJ District Office)

HFV-135:GAComyn:5/27/98:594-1648

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