Date of Approval Letters: March 28, 1996 (SAFE-GUARD® Suspension 10%)
November 21, 1996 (PANACUR® Suspension 10%)

CORRECTED FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 128-620

PANACUR®, and SAFE-GUARD® (fenbendazole) Suspension 10% for Beef and Dairy Cattle

"...effectively removes and controls infections in cattle due to *Dictyocaulus viviparus*, stomach worms, and intestinal worms"

Sponsored by:

Hoechst Roussel Vet

I. GENERAL INFORMATION

NADA Number:	128-620
Sponsor:	Hoechst Roussel Vet 30 Independence Boulevard P.O. Box 4915 Warren, NJ 08876-1258
Established Name:	fenbendazole
Trade Names:	SAFE-GUARD® Suspension 10% PANACUR® Suspension 10%
Dosage Form:	oral suspension
Marketing Status:	SAFE-GUARD® - over-the-counter PANACUR® - prescription
Pharmacological Category:	antiparasitic
Effect of Supplements:	These supplements provide for the use of SAFE-GUARD® Suspension 10% and PANACUR® Suspension 10% for the removal and control of gastrointestinal parasites and lungworm in a new class of cattle, dairy cattle of breeding age.

II. INDICATIONS FOR USE AND RECOMMENDED DOSAGE

Cattle, including dairy cows of breeding age

5 mg/kg (2.3 mg/lb) dose for the removal and control of:

- Lungworm: *Dictyocaulus viviparus*
- Stomach worms (adults):

  Ostertagia ostertagi (brown stomach worm)

- Stomach worms (adult and 4th stage larvae)

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

- Intestinal worms (adult and 4th stage larvae)

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

Beef Cattle (PANACUR® Suspension 10% only):

10 mg/kg (4.6 mg/lb) dose for the removal and control of:

- Stomach Worm 4th stage inhibited larvae *(Ostertagia ostertagi*) Type II Ostertagiasis
- Tapeworm *(Moniezia benedeni)*

III. EFFECTIVENESS

Effectiveness was established originally under NADA 128-620 and its supplement (48 FR 42809; September 20, 1983, and 53 FR 40058; October 13, 1988). No new studies were conducted to establish effectiveness associated with the use of fenbendazole in dairy cattle of breeding age.

IV. TARGET ANIMAL SAFETY

Animal safety was established originally under NADA 128-620 and its supplement (48 FR 42809; September 20, 1983, and 53 FR 40058; October 13, 1988). No new studies were conducted to establish animal safety associated with 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. Safe Concentrations and Tolerances

Safe concentrations for fenbendazole total residues in cattle tissues were established with the original NADA 128-620 and are listed below, along with the tissue consumption factors that were used:

Tissue	Safe Concentration
muscle	5 ppm
liver	10 ppm (factor of 2)
kidney	15 ppm (factor of 3)
fat	20 ppm (factor of 4)

The tolerance and marker residue for fenbendazole in cattle also were assigned with the original approval of NADA 128-620. The tolerance in cattle liver (the target tissue) is 0.8 ppm parent fenbendazole (the marker residue) as measured by the regulatory assay.

Newly established with this supplement are a safe concentration and a tolerance for residues of fenbendazole in milk. The safe concentration for fenbendazole total residues in milk is set at 1.67 ppm (1/3 of the 5 ppm safe concentration in

muscle tissue). The 1.67 ppm value was determined using FDA's approach to assigning safe concentrations based on food factors (44 FR 17070, March 20, 1979).

As explained in Part C below, the marker residue for fenbendazole in milk is the sulfoxide of parent fenbendazole. The tolerance is assigned at 0.6 ppm, although the marker residue never reaches that level in the milk from cattle treated at the approved dosing rate of 5 mg/kg body weight. The tolerance value was calculated from the marker residue to total residue percentage when total fenbendazole residues are at a maximum in milk. That maximum occurs in the range of 24 to 36 hours following dosing, and at that time, the sulfoxide represents approximately 35% of the total residue present. Accordingly, the tolerance for the fenbendazole sulfoxide in cattle milk is set at 0.6 ppm (35% of the 1.67 ppm safe concentration).

C. Milk Total Residue and Metabolism Study: LAV# 1506 SVM (Jan. 1992 to Aug. 1993)

This study was designed to determine the total residue profile as a function of time, to identify metabolites of fenbendazole in milk, and to select a marker substance to monitor residues in milk of lactating dairy cows.

Study Director: Dr. Steven Barker, School of Veterinary Medicine, Louisiana State University

Study Animals: 6 lactating Holstein cows, 33 mo. to 7 yrs old, averaging 603 kg body weight

Test Article and Dosage: ^{14}C-fenbendazole 1.89 mCi/g in aqueous suspension administered at a dose of 5.0 mg/kg as a single dose, *via* stomach tube

A morning milk sample obtained from each cow prior to treatment served as a blank control for the study. Following this milking, five of the cows received the test article. The sixth cow (control) did not receive fenbendazole. Morning and afternoon milk samples were collected for 6 days following drug administration.

Total residues for each whole milk sample were determined by scintillation counting in triplicate assay. Selected samples were also centrifuged, and 0.5 mL aliquots of fat and water portions were counted to determine label distribution. For metabolic profiling, milk samples were extracted by matrix solid phase dispersion (MSPD) techniques, and the absolute recovery of total label was determined by scintillation counting of the extracts. The distribution of the extracted label between remaining parent drug and metabolites was determined by HPLC analyses using UV diode array and in-line radiolabel detection. The identity of radiolabeled peaks was matched with known standards for the metabolites of fenbendazole based on retention time and UV-diode array spectra. Samples were also assayed quantitatively by HPLC using an internal (mebendazole) standard and correcting for recovery.

The results from the radiolabel assay for total residues in whole milk and the HPLC analyses of metabolites in whole milk averaged for the five cows as a

function of time are presented in Table 5.1.

Table 5.1. Average concentrations (+/- sd) of total residues and sulfoxide (FBZ-SO) and sulfone (FBZ-SO_2) metabolites of fenbendazole (FBZ) in whole milk and FBZ sulfoxide to total FBZ ratio percent as a function of time following oral administration of 5.0 mg fenbendazole/kg body weight to five lactating dairy cows

Day	**Milking**	**Total Residue (mcg/mL)**	**FBZ-SO (mcg/mL)**	**FBZ-SO_2 (mcg/mL)**	**FBZ-SO/total FBZ residue x 100**
Day 1	AM	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000
Day 1	PM	0.060 (0.043)	0.026 (0.025)	0.000 (0.000)	43.333
Day 2	AM	0.482 (0.076)	0.232 (0.045)	0.018 (0.011)	48.133
Day 2	PM	0.526 (0.111)	0.186 (0.005)	0.024 (0.013)	35.361**
Day 3	AM	0.408 (0.102)	0.158 (0.026)	0.062 (0.016)	38.725
Day 3	PM	0.298 (0.086)	0.088 (0.034)	0.046 (0.033)	29.530
Day 4	AM	0.186 (0.080)	0.030 (0.030)	0.046 (0.024)	16.129
Day 4	PM	0.108 (0.044)	0.006 (0.013)	0.014 (0.017)	5.555
Day 5	AM	0.054 (0.030)	0.000 (0.000)	0.010 (0.017)	0.000
Day 5	PM	0.024 (0.015)	0.000 (0.000)	0.000 (0.000)	0.000
Day 6	AM	0.012 (0.008)	0.000 (0.000)	0.000 (0.000)	0.000
Day 6	PM	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000

**Ratio percent used to calculate tolerance level.

At all times following administration of fenbendazole to lactating dairy cattle, residues in milk of fenbendazole and its metabolites were below the established safe concentration, and the total residue was evenly distributed between the fat and aqueous fractions of the whole milk. All residue levels were below the target of 0.83 ppm for the 1X tracer study (one-half the 1.67 ppm established safe concentration). No residues were detected in milk from the placebo (control) cow.

Metabolic profiling of the total residues indicated that the concentration of parent drug in milk was negligible. The sulfoxide and sulfone metabolites of fenbendazole were the compounds that contributed to milk residues. The sulfoxide metabolite of fenbendazole was established as the marker residue as it was present at levels significantly higher than parent fenbendazole or its sulfone metabolite. No other metabolites of fenbendazole were found in milk.

Milk Tolerance Calculation

In Table 5.1 above, the ratio percent value of fenbendazole sulfoxide, the marker residue, to total residues was 35.4% at 36 hours following fenbendazole administration. At this time total residues in milk were greatest. The tolerance was calculated by multiplying the ratio percent of fenbendazole sulfoxide to total

residues by the safe concentration (1.67 ppm). The tolerance was established to be 0.6 ppm (600 ppb).

D. Calf Tissue Total Residue Study: LAV# 1507 SVM (Apr. 1992 to Aug. 1993)

This study was conducted to measure residues in calves born to ^{14}C fenbendazole-treated dairy cattle. Total residue profiles in calf liver, kidney, fat, and muscle were measured to provide data demonstrating the extent to which fenbendazole and its metabolites are transferred to and retained by the tissues of calves born to fenbendazole-treated cows.

Study Director: Dr. Steven Barker, School of Veterinary Medicine - Louisiana State University

Study Animals: 6 pregnant Holstein cows, 3 yrs or older, averaging 616 kg body weight

Test Article and Dosage: ^{14}C-fenbendazole 1.89, 1.95, and 2.09 mCi/g in aqueous suspension administered at a dose of 5.0 mg/kg as a single dose, *via* stomach tube

Five days prior to anticipated calving, five pregnant Holstein cows were administered an aqueous suspension of ^{14}C-labeled and unlabeled fenbendazole containing approximately 2 mCi activity/g by stomach tube at a dose calculated to equal 5.0 mg/kg body weight. A sixth pregnant cow was administered carrier with no fenbendazole and was the control for the study. Four calves (one from the control cow and three from treated cows) were delivered by cesarean section approximately 70 hours after dosing. The remaining two treated cows calved naturally (1 calf each) at 4 and 25 hours post-dosing. A treated calf died 5 hours after delivery. Three of the four remaining treated calves and the control calf were sacrificed 24 hours after delivery. The other treated calf was sacrificed 48 hours after delivery. Surviving calves received colostrum from treated dams and milk replacer as needed for 24 to 48 hours up to time of sacrifice.

Total residues for the described tissues were determined by oxidation of 0.5 g tissue samples in triplicate and scintillation counting and are summarized in Table 5.2.

Table 5.2.: Mean concentrations (+/- sd) of total residues of fenbendazole and metabolites in calf tissues following administration of 5.0 mg fenbendazole/kg body weight to five pregnant dairy cows.

Tissue	**Total Residue (mcg/g)**
liver	1.398 (0.998)
kidney	0.528 (0.383)
fat	0.386 (0.400)
muscle	0.306 (0.236)

For metabolic profiling, liver tissue from one calf was extracted by matrix solid phase dispersion (MSPD) techniques, and the absolute recovery of total label was determined by scintillation counting of the extracts. The distribution of the extracted label between parent drug and metabolites was determined by HPLC analyses using UV diode array and in-line radiolabel detection. The identity of radiolabeled peaks was matched with known standards for the metabolites of fenbendazole based on retention time and UV-diode array spectra.

Results indicated that the label was distributed between the sulfone (34%) and sulfoxide (58%) metabolites of fenbendazole and parent fenbendazole (8%). No other radiolabeled metabolites were observed in the liver. Profiles of kidney, fat, and muscle tissue from all calves using HPLC indicated the presence of the sulfoxide and sulfone metabolites. The parent drug, fenbendazole, was present in trace quantities. No other metabolites were indicated by the assay.

From these residue data it was concluded that, in calves born to and consuming colostrum from fenbendazole-treated dams, residues of fenbendazole in edible tissues were below the established safe concentrations. Residue levels in liver, kidney, fat, and muscle as a percent of the safe concentrations were 13.98%, 3.52%, 1.93% and 6.12%, respectively. Therefore, edible tissues of calves born to fenbendazole-treated dams is safe even when fenbendazole is administered prior to parturition.

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

This study, using non-radiolabeled fenbendazole, 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. A further objective was to determine whether incurred fenbendazole residues or its metabolites demonstrate activity in three commonly used milk antibiotic screening tests: Charm II assay, Delvotest P, and *Bacillus stearothermophilis* disc assay (BSDA).

Study Director: Dr. Steven Barker, School of Veterinary Medicine, Louisiana State University

Test Article Administration: fenbendazole 10% suspension, administered at 5.0 mg/kg as a single dose, *via* stomach tube

Study Animals: 11 lactating Holstein cows, average 505 kg body weight, milking ≥ 20 kg/day

The ten treated cows received fenbendazole 10% suspension in 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 were collected at that milking and were used as blank controls for the study. Milk samples (100 mL) were then collected 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 analyses 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 10% suspension at a dose of 5.0 mg/kg body weight to lactating dairy cows 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. Peak fenbendazole sulfoxide marker level was 0.12 ± 0.03 mcg/mL (Table 5.3). No residues of fenbendazole were detected in the control cow.

Table 5.3. Mean concentrations (+/-sd) of fenbendazole and marker metabolites in whole milk as a function of time following oral administration of a 10% suspension at a rate of 5.0 mg/kg body weight to ten lactating dairy cows.

time (hours) after dosing	**fenbendazole (mcg/mL)**	**fenbendazole sulfoxide** (mcg/mL)**	**fenbendazole sulfone (mcg/mL)**
0	nd*	nd	nd
12	nd	0.08 (0.06)	0.00 (0.00)
24	nd	0.12 (0.03)	0.04 (0.01)
36	nd	0.08 (0.03)	0.06 (0.01)
48	nd	0.03 (0.02)	0.05 (0.01)
60	nd	0.01 (0.01)	0.02 (0.01)
72	nd	0.00 (0.00)	0.00 (0.00)

*No residues detected; **Marker residue

Antibiotic residue test screening was conducted on milk samples from three 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 oral suspension at 5 mg/kg bodyweight 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 Subsections C and E, above, demonstrate 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 (PANACUR®, SAFE-GUARD® Suspension 10%), at the 5 mg fenbendazole/kg dose, in dairy cattle of breeding age.

The 8-day preslaughter withdrawal time established in the original approval of NADA 128-620 (48 FR 42809; September 20, 1983) as codified at 21 FR 520.905a applies to lactating dairy cows treated with fenbendazole 10% suspension.

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 SAFE-GUARD® (fenbendazole) Suspension 10% and PANACUR® (fenbendazole) Suspension 10%, when administered per os 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 42810; Sept. 20, 1983) allowed the establishment of a safe concentration of 1.67 ppm for total residues of fenbendazole in milk. Based on submitted residue and metabolite data, a tolerance of 0.6 ppm for residues in milk of fenbendazole sulfoxide (the marker residue) is established. Because the maximum levels of residues found in milk of fenbendazole-treated cattle were well below the safe concentration and tolerance noted above, no discard of milk (zero milk withdrawal) is required. The slaughter withdrawal time of 8 days required for treated dairy cattle of breeding age is the same as that established for cattle under the original NADA 128-620.

Federal law restricts PANACUR® Suspension 10% for Cattle to use by or on order of a licensed Veterinarian. The decision to keep PANACUR® Suspension 10% as a prescription product was made in 1988, based on the approval of the 10 mg/kg body weight dose for beef cattle (53 FR 40058; October 13, 1988). The 10 mg/kg dose is

not for use in dairy cows of breeding age due to potential for violative milk residues. SAFE-GUARD® Suspension 10% is marketed as an over-the-counter (OTC) product. The decision to keep SAFE-GUARD® Suspension 10% as an OTC product was made in 1988, based on the fact that it would not carry the 10 mg/kg dose on its label.

In accordance with 21 CFR 514.106(b)(2), these are Category II changes. The approval of these changes did not require reevaluation of the safety and effectiveness data in the parent application.

The agency has determined under 21 CFR 25.33(d)(5) that these actions are of a type that do 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 Labeling (Attached)

PANACUR® (fenbendazole) Suspension 10% - 33.8 oz (1000 mL) bottle label
PANACUR® (fenbendazole) Suspension 10% -1-gallon (3785 mL) container label
SAFE-GUARD® Suspension 10% - 1-pint 0.9 oz (500 mL) bottle label
SAFE-GUARD® Suspension 10% - 33.8 fl. oz (1000 mL) bottle label
SAFE-GUARD® Suspension 10% -1-gallon (3785 mL) container label

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d).