Approval Date: March 14, 2003

FREEDOM OF INFORMATION SUMMARY

Supplemental NADA

131-675

Safe-Guard® Dewormer 20% Type A medicated article
(fenbendazole)

An additional claim for Safe-Guard® Dewormer 20% Type A medicated article adding: "for the control of large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris, Triodontophorus* spp.), small strongyles (*Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp.), pinworms (*Oxyuris equi*), and ascarids (*Parascaris equorum*) in horses.

Intervet Inc.
405 State Street
P.O. Box 318
Millsboro, DE 19966-0318

TABLE OF CONTENTS

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

a. NADA Number: 131-675

b. Sponsor: Intervet, Inc.
405 State Street
P.O. Box 318
Millsboro, DE 19966-0318

Drug Labeler Code: 057926

c. Established Name: fenbendazole

d. Proprietary Name: Safe-Guard® Dewormer 20% (fenbendazole) Type A Medicated Article

e. Dosage Form: Type A medicated article

f. How Supplied: 25 lb. (11.34 kg) bag

g. How Dispensed: Over the counter (OTC)

h. Amount of Active Ingredient: 200 grams per kilogram (90.7 grams per pound)

i. Route of Administration: Oral

j. Species/Class: Horses/Equine

k. Recommended Dosage: For the control of large strongyles, small strongyles, and pinworms, the recommended dose is 5 mg fenbendazole per kg body weight (2.27 mg/lb) in a one day treatment. For the control of ascarids, the recommended dose is 10 mg fenbendazole per kg body weight (4.54 mg/lb) in a one day treatment.

Regular deworming at intervals of six to eight weeks may be required due to the possibility of reinfection. A veterinarian should be consulted for assistance in the diagnosis, treatment, and control of parasitism.

Safe-Guard® Dewormer 20% (fenbendazole) Type A medicated article should be diluted before addition to the ration. A dilution of one part of Safe-Guard®

Type A medicated article and nine parts of grain carrier is the suggested working premix. The working premix is then blended with the complete feed mixture. Both the working premix and complete feed should be thoroughly mixed to ensure complete and uniform distribution of the product.

l. Pharmacological Category: Anthelmintic

m. Indications: Safe-Guard® Dewormer 20% (fenbendazole) Type A medicated article is indicated for the control of large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris, Triodontophorus* spp.), small strongyles (*Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp.), pinworms (*Oxyuris equi*), and ascarids (*Parascaris equorum*) in horses.

n. Effect of Supplement: This supplement to NADA 131-675 provides for a new claim for control of gastrointestinal worms in horses [large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris, Triodontophorus* spp.), small strongyles (*Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp.), pinworms (*Oxyuris equi*), and ascarids (*Parascaris equorum*)].

II. EFFECTIVENESS

A. Dosage Characterization:

The dose and duration of fenbendazole for the control of large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris, Triodontophorus* spp.), small strongyles (*Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp.), pinworms (*Oxyuris equi*) at 5 mg/kg (2.27 mg/lb) body weight as a one day treatment, and for the control of ascarids (*Parascaris equorum*) at 10 mg/kg (4.54 mg/lb) as a one day treatment in horses, was established in the original approval of 10% fenbendazole suspension under NADA 128-620.

B. Substantial Evidence:

Study Title: Clinical Endpoint Bioequivalence Study in Equines to Compare the Effectiveness of Fenbendazole Pellets (0.5%) and Fenbendazole Suspension (10%) Administered Orally

Clinical Investigator: Dr. Allan J. Paul, DVM, MS, University of Illinois, College of Veterinary Medicine, 2001 South Lincoln Avenue, Urbana, Illinois 61801

Purpose of Study: To demonstrate bioequivalence of two orally administered formulations of fenbendazole at a dose rate of 5.0 mg/kg body weight in horses naturally infected with adult large and small strongyles.

Study Design: A clinical endpoint study was conducted in horses naturally infected with large and small strongyles, to establish the bioequivalence of the proposed 20% fenbendazole Type A medicated article (fed as a 0.5% fenbendazole top dress, a Type C medicated feed) to an approved 10% fenbendazole suspension (Panacur® NADA 128-620).

Thirty (30) horses were ranked in descending order on a basis of fecal egg counts (eggs per gram, [epg]) and assigned to replicate groups of three (3) horses. The presence of large and small strongyles were confirmed by coproculture. Horses within each replicate were randomly assigned to the treatment and control groups. Horses were housed three per pen by replicate for the duration of the study. The two treatment groups and the control group each comprised 10 horses. The mixed breed horses (17 females, 13 males) were one to four years of age and weighed between 214 and 384 kg at the start of the study. The 10% suspension formulation was administered orally by dose syringe and the 0.5 % pellets were top dressed on a feed container mixed with oats. Both fenbendazole formulations were given at a dose rate of 5.0 mg/kg body weight as a single oral dose. The control group received non-medicated pellets.

Data collected during the study included: time and amount of formulation consumed or dosed, reaction of animals to dosing and during treatment, fecal egg counts before the start of the study and at necropsy, and post-mortem counts of adult stages of large strongyles, small strongyles and pinworms from the contents of the large intestine.

Effectiveness was calculated as the percentage (%) reduction in geometric mean (GM) worm burdens of the fenbendazole treated groups relative to the control animals as follows:

$$\text{Effectiveness \%} = \frac{GMc - GMt}{GMc} \times 100$$

GMc = Geometric mean number of parasites in control horses.

GMt = Geometric mean number of parasites in treated horses

Study Results: Fecal egg output was significantly reduced by >98% in both treatment groups ($P<0.0001$). Effectiveness against the pivotal parasites, namely, *S. edentatus*, *S. vulgaris* and cyathostomes was 97-100% for both formulations. Differences in effectiveness between the two formulations were not significant thus demonstrating bioequivalence. There were no adverse reactions related to the treatments.

Strongyle adult worm counts of the target species for determining bioequivalence of the two formulations, namely cyathostomes, *Strongylus edentatus,* and *Strongylus vulgaris,* at postmortem were analyzed for differences using Analysis of Variance Method (PROC GLM) at the 5% significance level. The effectiveness of the two formulations of fenbendazole for controlling these parasites was not significantly different, thus demonstrating that the two formulations are bioequivalent. The results of the effectiveness study are presented below.

Table 1 - Group Geometric Mean Fecal Egg Counts (epg)[1] Before & After Treatment & Effectiveness (%)

Group	Number Animals	Pre-Treatment Geometric mean	Post Treatment Geometric Mean	% Reduction (pre/post treatment)
0.5% Pellets	10	146.41	1.42	99.03
10% Suspension	10	146.52	2.71	98.15
Control	10	151.08	312.91	-

(1) epg = eggs per gram

Table 2: Group Geometric Mean Adult Worm Counts of Treated & Control Horses at Necropsy & Efficacy(%): Pivotal Data *

Parasite	Treatment Group	Geometric Mean	% Reduction	*P*-value Suspension vs. Pellets
Small Strongyles (Cyathostomes)	1. Pellets 2. Suspension 3. Control	1.50 0.64 101.28	98.52 99.37 -	0.5386
Strongylus edentatus	1. Pellets 2. Suspension 3. Control	0.00 0.00 18.18	100 100 -	1.00
Strongylus vulgaris	1. Pellets 2. Suspension 3. Control	0.28 0.00 13.67	97.95 100 -	0.6625

*70% or more of the control horses infected

Study Conclusions:
A 0.5 % fenbendazole pelleted ration, formulated from the 20% Type A medicated article was readily consumed by horses and was well tolerated. Effectiveness against the target adult parasites, namely, Cyathostomes, *S. edentatus* and *S. vulgaris* was in excess of 97%. Analysis of the parasite burdens of the horses given the pellet formulation and those given the 10% suspension formulation showed that there were no significant differences in anthelmintic activity between the two formulations, thus demonstrating that both formulations were clinically bioequivalent.

III. TARGET ANIMAL SAFETY

The safety of fenbendazole administration to horses was established in the original approval for the 10% fenbendazole oral suspension under NADA 128-620. No new safety studies were conducted in support of this supplemental approval.

IV. HUMAN SAFETY

Data on human safety pertaining to the consumption of drug residues in food were not required for approval of this NADA. This drug is labeled for use in horses which are non-food animals. The following "Residue Warning" statement appears on the product label: "Do not use in horses intended for food." Regarding human safety relative to possession, handling and administration, a "Warning" statement appears on the product label as follows: "Keep this and all medication out of the reach of children. Not for use in humans."

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21CFR Section 514 of the implementing regulations. The data demonstrate that Safe-Guard® Dewormer (fenbendazole) 20% Type A medicated article is safe and effective when used under labeled conditions.

The drug is labeled for over the counter use. Routine deworming of horses is a widely accepted and recommended practice performed by the layperson. The product labeling contains detailed information on use deemed to be adequate for the layperson.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new claim for control of gastrointestinal worms in horses, for which the supplemental application was approved.

VI. ATTACHMENTS

Labeling is attached as indicated below:

Type A medicated article bag label
Type B medicated feed specimen (Blue Bird) label
Type C medicated feed specimen (Blue Bird) label