Approval Date: May 28, 1985

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 120-648

B. Sponsor

Hoechst Roussel Vet
30 Independence Blvd.
P.O. Box 4915
Warren, NJ 07059

C. Proprietary Name

Panacur ® and Safe-Guard®

D. Established Name

fenbendazole

E. Dosage Form

Paste

F. Dispensing Status

Over the Counter (OTC)

G. Dosage Regimen

Fenbendazole Paste 10% is administered orally at a rate of 2.3 mg/lb (5 mg/kg) for the control of large strongyles, small strongyles (cyathostomes), and pinworms. For foals and weanlings (less than 18 months of age) where ascarids are a common problem, the recommended dose is 4.6 mg/lb (10 mg/kg). For control of encysted early third stage (hypobiotic), late third stage and fourth stage mucosal cyathostome larvae and 4th stage larvae of *Strongylus vulgaris*, the recommended dose is 4.6 mg/lb (10 mg/kg) daily for 5 consecutive days.

H. Route of Administration

Oral

I. Indication

Fenbendazole Paste 10% is indicated for the control of large strongyles (*Strongylus edentatus*, *S. equinus*, *S. vulgaris*), small strongyles (cyathostomes) including encysted early 3rd stage (hypobiotic), late third stage and fourth stage mucosal cyathostome larvae, pinworms (*Oxyuris equi*), ascarids (*Parascaris equorum*), and arteritis caused by 4th stage larvae of *Strongylus vulgaris* in horses.

Fenbendazole Paste 10% is approved for use concomitantly with an approved form of trichlorfon. Trichlorfon is approved for the treatment of stomach bots

(*Gasterophilus spp*.) in horses. Refer to the manufacturer's label for directions for use and cautions for trichlorfon.

J. Effect of Supplement

For treatment of encysted mucosal cyathostome (small strongyle) larvae including hypobiotic early third stage, late third stage and fourth stage larvae at 10 mg/kg/day for 5 consecutive days.

II. EFFECTIVENESS

A series of well controlled efficacy studies was submitted with the original NADA 120-648 and also with supplements to the original NADA 120-648. For this supplemental application, additional efficacy studies were conducted and are summarized below.

Well controlled trials were conducted at three different geographical locations in the United States in naturally infected horses to determine the efficacy of fenbendazole against encysted mucosal cyathostome larvae.

On each site, twenty (20) horses were assigned, by restricted randomization, to treatment and control groups, each comprising 10 horses. Fenbendazole 10% paste, was administered orally to the horses in the treatment groups at a dose rate of 10 mg/kg body weight for 5 consecutive days.

Following a minimum six week post-treatment housing period, the horses were euthanized and their cyathostome worm burdens assessed. Encysted hypobiotic early 3rd stage larvae (EL3) were identified and enumerated following pepsin HCl digestion of the large intestinal mucosa. The larger encysted late L3 and L4 were enumerated following transmural illumination (TMI) and digestion. Efficacy was calculated as the percentage (%) reduction in geometric mean (GM) worm burdens of the fenbendazole treated groups relative to the controls as follows:

$$Efficacy\ (\%) = \frac{GMc - GMt}{GMc} \times 100$$

GMc = mean number of strongyles in control horses.

GMt = mean number of strongyles in treated horses

Strongyle larval and adult worm counts at post-mortem were analyzed for differences using the parametric two-sample t-test and the 5% significance level. (When the t-test was inappropriate due to zero variances, where indicated it was possible to use the non-parametric Fisher exact test). Data were found to be suitably transformed for parametric analyses using the log (X+1) transformation. The results from the three sites were pooled and analysis carried out for an overall treatment effect using analysis of variance and the randomized block design. In the analyses, studies and study by treatment effects were treated as random effects and treatments as a fixed effect, and analyses were carried out on log (X+1) transformed data using a mixed effects model.

Five consecutive treatments with fenbendazole provided >92% efficacy for the different mucosal cyathostome larvae stages listed in the INDICATIONS section. Data for the three studies support the use of fenbendazole, applied orally, at 10 mg/kg daily for 5

days of the treatment of all stages of encysted cyathostome larvae in the mucosa of the large intestine of horses.

A. Dose Confirmation of Efficacy Against Cyathostome Larvae Encysted In The Large Intestinal Mucosa

a. Study Type

Controlled necropsy studies to demonstrate efficacy against encysted mucosal cyathostome larvae in naturally infected horses. There were three studies.

b. Investigators

1. Site 1- Study Number 120-648-01-02-95-SP

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University of Illinois
College of Veterinary Medicine
2001 South Lincoln Avenue
Urbana, Illinois 61801

2. Site 2 - Study Number 120-648-02-02-95-SP

Thomas R. Klei, Ph.D.
Department of Veterinary Science
Louisiana Agricultural Experiment Station
LSU-Agricultural Center
Louisiana State University
Baton Rouge, LA 70803-8416

3. Site 3 - Study Number 120-648-03-02-95-SP

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Department of Comparative Medicine
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Knoxville, TN 37996-1071

c. General Design

1. Purpose:

To confirm the efficacy of orally administered fenbendazole at10 mg/kg daily for 5 days against naturally acquired cyathostome infections in particular, mucosal 3rd and 4th stage larvae.

2. Animals:

The studies included a total of 30 horses/ponies treated with fenbendazole and a total of 30 control horses/ponies. The mixed breed horses and ponies were aged between 7 months and three years and weighed between 65 and 398 kg at the study start.

3. Housing:

The horses/ponies were housed in their treatment groups (2-5/pen) for the duration of the study to preclude further infection.

4. Infections:

These were acquired while at pasture. This was confirmed prior to the start of the studies by fecal examinations and coproculture of the test horses and by post-mortem larval worm counts of three (3) "tracer" horses/ponies at each site.

5. Dosage form:

A paste containing 100 mg fenbendazole/g paste.

6. Route:

By dosing syringe, administering the paste orally on the dorsum of the tongue.

7. Dose:

10 mg fenbendazole/kg body weight for 5 ***consecutive*** days.

8. Study Duration:

The horses/ponies were necropsied for nematode recovery starting on day 43 of the study.

9. Relevant Parameters Measured:

Early 3rd stage, late 3rd stage and 4th stage cyathostome larvae encysted in the mucosa of the large intestine using transmural illumination (TMI) and digestion techniques. For TMI, uniform sections of mucosa were collected from the caecum, ventral and dorsal colons and stretched over a light source. Encysted cyathostome larvae (late L3/L4) were enumerated using a microscope at 10-15 X magnification. For digestion, uniform sections of mucosa were collected from the three organs.The mucosa and submucosa were separated from the serosa and transferred to suitable containers for subsequent digestion with a pepsin HCl mixture at 37° C for at least 2 hours. Aliquots of the digested mixture were stained then examined by stereomicroscopy (X20) for early 3rd stage, late L3 and L4 cyathostome larva:adults/larvae in the gut lumen.

d. Pooled Data Results

Efficacy against all stages of encysted mucosal cyathostome larvae was >90%.

Site 1

Stage	Mean (GM) Count		
	Control	**Fenbendazole**	**% Efficacy**
Mucosal EL_3 (hypobiotic)	1510.4	63.8	96 (p=0.0628)
Mucosal LL_3/L_2 (by digestion)	2482.9	62.4	98 (p=0.0044)
Mucosal LL_3/L_4 (by TMI)	137.8	2.4	98 (p=0.0001)
Lumen adults / Larvae	5423.3	184.4	97 (p=0.0001)

Site 2*

Stage	Mean (GM) Count		
	Control	**Fenbendazole**	**% Efficacy**
Mucosal EL_3 (hypobiotic)	23861.8	2150.9	91 (p<0.0001)
Mucosal LL_3/L_2 (by digestion)	1409.1	89.9	94 (p=0.0485)
Mucosal LL_3/L_4 (by TMI)	2752.9	698.7	75 (p=0.0066)
Lumen adults / Larvae	26598.1	8346.8	69 (p=0.0325)

*Benzimidazole (BMZ) resistant parasites present

Site 3

Stage	Mean (GM) Count		
	Control	**Fenbendazole**	**% Efficacy**
Mucosal EL_3 (hypobiotic)	4944.9	6.2	99.9 (p<0.0001)
Mucosal LL_3/L_2 (by digestion)	1727.9	47.3	97.3 (p=0.0083)
Mucosal LL_3/L_4 (by TMI)	7415.5	705.1	90.5 (p<0.0001)
Lumen adults / Larvae	82,689.1	6203.7	92.5 (p<0.0001)

Pooled Data (3 sites)

Stage	Mean (GM) Count		
	Control	**Fenbendazole**	**% Efficacy**
Mucosal EL_3 (hypobiotic)	5628.2	99.1	98 (p=0.0433)
Mucosal LL_3/L_2 (by digestion)	1821.7	64	97 (p<0.0001)
Mucosal LL_3/L_4 (by TMI)	1414.5	117.7	92 (p=0.0339)
Lumen adults / Larvae	22,849.2	2124.5	91 (p=0.0336)

e. Adverse Reactions

There were no adverse reactions to treatment.

f. Conclusions

Fenbendazole administered orally at 10 mg/kg for 5 consecutive days to horses/ponies with naturally acquired cyathostome infection is safe and effective.

III. TARGET ANIMAL SAFETY

The safety of fenbendazole in the horse was evaluated in the original NADA approval. No new safety studies were required for this supplemental NADA.

IV. HUMAN FOOD SAFETY

The label for fenbendazole 10% paste will carry a warning statement "Do not use in horses intended for food". Consequently, the drug is not expected to enter the food chain.

V. AGENCY CONCLUSIONS

The data in support of this supplemental NADA satisfy the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrate that PanacurÒ /SafeguardÒ (fenbendazole), when used under the labeled conditions of use, is safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the additional claim to include the treatment of encysted small strongyles. This approval relied upon the safety and effectiveness data in the parent application and evaluation of new efficacy data submitted in the supplemental application.

The drug is labeled for Over the Counter use. Routine deworming of horses is a widely accepted and recommended practice performed by the layperson. A diagnosis of parasite infection prior to deworming is not necessary.

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 treatment of encysted cyathostomes for which the supplemental application was approved.

VI. LABELING

Package insert
Syringe labels 25 g & 92 g

Product Labeling: Submissions G0056 & S0060 provide for product labeling.
The order of the product labeling which follows is:

Panacur 92 g syringe -label
Panacur 92 g syringe -package insert
Safe-Guard 92 g syringe - label
Safe-Guard 92 g syringe - package insert

Panacur 25 g syringe- label
Panacur 25 g syringe- syringe box label (package insert)*
Safe-Guard 25 g syringe - label
Safe-Guard 25 g syringe - syringe box label (package insert)*

*The package insert is no longer included in the box containing the 25 g syringes; however, the information on the package insert now appears on the box label which contains the 25 g syringe.

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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). The content of this document has not changed.