Approval Date: April 18, 1990

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-819

B. Sponsor

Pfizer Inc.
235 East 42nd St.
New York, New York 10017

C. Proprietary Name

Strongid 48

D. Established Name

pyrantel tartrate

E. Dosage Form

Pyrantel tartrate is formulated in a feed premix at a concentration of 10.6% (48 grams per pound) as pyrantel tartrate.

F. Dosage Regimen

Pyrantel tartrate is to be administered on a daily basis at the rate of 1.2 mg/lb (2.64 mg/kg) body weight daily. The duration of administration is for the period during which the animal is at risk of exposure to internal parasites.

G. Route of Administration

To be administered orally in the feed as either a top dress or mixed in the horses daily grain ration.

H. Indication

For the prevention of Strongylus vulgaris larval infections in horses.

For control of the following parasites in horses:

- LARGE STRONGYLES (adults) *S. vulgaris*, *S. edentatus*, *Triodontophorus* spp.
- SMALL STRONGYLES (adult and fourth-stage larvae) *Cyathostomum* spp. *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp., *Poteriostomum* spp.,
- PINWORMS (adult and fourth-stage larvae) *Oxyuris equi*
- ASCARIDS (adult and fourth-stage larvae) *Parascaris equorum*.

II. EFFECTIVENESS

A. Dose Titration Study (Pivotal)

Investigator:

Thomas J. Kennedy, PhD
AEF Research Inc.
Waunakee, Wisconsin 53597

A total of 32 worm free foals were used in a dose titration study to determine the optimum dose level of pyrantel tartrate administration in the feed on a daily basis for the prevention of *S. vulgaris* larval infections in horses. The animals were divided into the following treatment groups with 8 animals per group: T-1 non-medicated control; T-2 pyrantel tartrate 0.44 mg/kg; T-3 pyrantel tartrate 2.64 mg/kg; T-4 pyrantel tartrate 4.4 mg/kg. The medicated test animals were administered the drug in their feed on a daily basis for thirty consecutive days. All foals were euthanized at the conclusion of the study for assessment of the efficacy of the test article. Parameters measured included arterial lesion and adhesion scores, arterial wall thickness, larvae intimal tracks and number of larvae recovered. The arterial lesions and adhesions present at necropsy were evaluated based on a scoring system of 1 to 10 with 1 being normal and 10 being extremely severe lesions.

Each of the study parameters were first statistically analyzed by one-way analysis of variance along with application of the Box-Cox method for determining the appropriate transformation. Based on the Least-Significant-Difference comparisons of treatment means at a 5% level of significance, there was no significant difference between the non-medicated treatment (T-1) and the 0.44 mg/kg medicated group (T-2) in the lesion score, adhesion score, arterial wall thickness and number of tracks. For each of these response variables, pyrantel tartrate medicated foals at 2.64 mg/kg (T-3) and 4.40 mg/kg (T-4) were significantly different than the foals at the 0.44 mg/kg dose level and the non-medicated foals but were not significantly different from each other. The mean number of larvae for foals in the non-medicated treatment group was significantly higher than that for foals in each of the three pyrantel medicated treatment groups; however, the mean number of larvae was not significantly different among the three medicated treatment groups. Based on the above analysis and the results found in Table 1, the dose level of 2.64 mg/kg body weight was determined to be the optimum dose for the prevention of *S. vulgaris* larva infections.

Table 1 Summary of Necropsy Results for Dose Titration Study

Treatment	*S. Vulgaris* Artery Results - Lesion** Score	*S. Vulgaris* Artery Results - Adhesion** Score	*S. Vulgaris* Artery Results - Wall Thickness*	*S. Vulgaris* Artery Results - Number Tracks	*S. Vulgaris* Artery Results - Number Larvae
T-1	6.1	4.0	1.71	119.4	5.4
T-2	4.8	4.4	1.71	76.8	1.0
T-3	1.0	1.1	0.88	0.4	0.1
T-4	1.0	1.0	0.91	0.1	0.0
% Reduction - T-1 vs. T-2	27.1%	-12.5%	-0.1%	35.7%	81.6%
% Reduction - T-1 vs. T-3	100%	95.2%	48.6%	99.6%	97.4%
% Reduction - T-1 vs. T-4	100%	100%	46.5%	99.9%	100%

TREATMENT DESCRIPTION
T-1 = INFECTED NON-MEDICATED CONTROLS
T-2 = INFECTED PYRANTEL TARTRATE .44 MG/KG
T-3 = INFECTED PYRANTEL TARTRATE 2.64 MG/KG
T-4 = INFECTED PYRANTEL TARTRATE 4.40 MG/KG
***WALL THICKNESS IN MM**
****** **Lesion and Adhesion Score System**
1 = Normal artery 2-3 = Mild lesions 4-6 = Moderate lesions 7-8 = Severe lesions 9-10 = Extremely severe lesions

B. Dose Confirmation Study (Pivotal)

Investigator:

Thomas J. Kennedy, PhD
AEF Research Inc.
Waunakee, Wisconsin 53597

A study was conducted to confirm the efficacy of 2.64 mg/kg body weight of pyrantel tartrate when administered orally via feed to foals for the prevention of *S. vulgaris* larval infections. The treatment groups included dose levels of 0.0, 2.64, 1.98 mg/kg body weight. The dose level of 1.98 mg/kg was included in this study to confirm that feed containing the active drug at the lower end of the permissible assay variation (PAV) for pyrantel tartrate in feed would still be effective in preventing *S. vulgaris* larval infections. Twenty-four worm free foals were equally assigned to one of three treatment groups and experimentally infected with 1000 infective larvae of *S. vulgaris*. Foals in treatment groups T-2 (2.64 mg/kg) and T-3 (1.98 mg/kg) were fed daily a top dress pellet containing the pyrantel tartrate (9600 gm/ton) for 35 consecutive days. Foals in treatment group T-1 were non-medicated controls. All foals were necropsied at the conclusion of the study for assessment of the efficacy of the test article.

Efficacy was determined by collecting the following data; twice daily clinical observations, daily drug intake, weekly interval body weights, daily rectal body temperatures, necropsy observations of adhesions and lesion scores, arterial wall thickness, larva intimal tracks, and number of *S. vulgaris* larvae recovered. The arterial lesions and adhesions present at necropsy were evaluated based on a scoring system of one to five with one being normal and five being extremely severe lesions.

The results of this study found in Table 2 confirm that pyrantel tartrate at the dose of 2.64 mg/kg body weight daily is effective in the prevention of *S. vulgaris* larval infections in foals. There were no findings that suggested an adverse effect of pyrantel tartrate on foals.

Table 2 Summary of Necropsy Results for Dose Confirmation Study

TREATMENT	*S. VULGARIS* ARTERY RESULTS - LESION** SCORE	*S. VULGARIS* ARTERY RESULTS - ADHESION** SCORE	*S. VULGARIS* ARTERY RESULTS - WALL THICKNESS*	*S. VULGARIS* ARTERY RESULTS - NUMBER TRACKS	*S. VULGARIS* ARTERY RESULTS - NUMBER LARVAE
T-1	4.14	4.14	5.52	67.43	42.86
T-2	1.43	1.14	1.86	2.00	0.71
T-3	1.00	1.13	1.45	12.5	0.00
% **REDUCTION** - T-1 vs. T-2	86.3	95.5	66.3	97.0	98.3
% **REDUCTION** - T-1 vs. T-3	100	95.9	73.7	81.5	100

TREATMENT DESCRIPTION
T-1=INFECTED NON-MEDICATED CONTROL
T-2= INFECTED 2.64 MG/KG PYRANTEL TARTRATE DAILY
T-3 INFECTED 1.98 MG/KG PYRANTEL TARTRATE DAILY
*** LESION AND ADHESION SCORE SYSTEM:**
1=NORMAL 2=MILD LESION 3=MODERATE LESION 4=SEVERE LESION 5=EXTREMELY SEVERE LESION

C. Dose Comparison Study (Pivotal)

Investigator:

Thomas J. Kennedy, PhD
AEF Research Inc.
Waunakee, WI 53597

A dose comparison study was conducted to demonstrate the equivalent efficacy of two dosage forms (top dress and complete feed) of pyrantel tartrate when administered orally via feed to foals at the dose level of 2.64 mg/kg body weight daily for the prevention of *S. vulgaris* larval infections. Twenty four worm free foals were equally assigned to one of three treatment groups and experimentally infected with 1000 infective larvae of *S. vulgaris* . Foals in treatment groups T-2 (top dress, 9600 gm/ton pyrantel tartrate) and T-3 (complete feed, 1000 gm/ton pyrantel tartrate) were fed daily their respective dose forms containing the pyrantel tartrate

for 35 consecutive days. Foals in treatment group T-1 were non-medicated controls. All foals were necropsied at the conclusion of the study for assessment of the efficacy of the test article.

Efficacy was determined by collecting the following data; twice daily clinical observations, daily drug intake, weekly interval body weights, daily rectal body temperatures, *S. vulgaris* necropsy observations on adhesion and lesion scores, arterial wall thickness, larvae intimal tracks, and number of larvae recovered. The arterial lesions and adhesions present at necropsy were evaluated based on a scoring system of 1 to 5 with 1 being normal and 5 being extremely severe lesions.

The results of this study found in Table 3 demonstrate that pyrantel tartrate, at the dose level of 2.64 mg/kg body weight daily, is effective in the prevention of *S. vulgaris* larval infections in foals when fed daily in either of two dosage forms, top dress or in a complete grain mix. There were no findings that suggested an adverse effect of pyrantel tartrate on foals.

Table 3 Summary of Necropsy Results for Dose Comparison Study

TREATMENT	*S. VULGARIS* ARTERY RESULTS - LESION** SCORE	*S. VULGARIS* ARTERY RESULTS - ADHESION** SCORE	*S. VULGARIS* ARTERY RESULTS - WALL THICKNESS*	*S. VULGARIS* ARTERY RESULTS - NUMBER TRACKS	*S. VULGARIS* ARTERY RESULTS - NUMBER LARVAE
T-1	4.14	4.14	5.52	67.43	42.86
T-2	1.43	1.14	1.86	2.00	0.71
T-3	1.00	1.00	1.39	0.13	0.00
% **Reduction** - T-1 vs T-2	86.3	95.5	66.3	97.0	98.3
% **Reduction** - T-1 vs T-3	100	100	74.8	100	99.7

TREATMENT DESCRIPTION
T-1= INFECTED NON-MEDICATED CONTROL
T-2=INFECTED 2.64 MG/KG PYRANTEL TARTRATE DAILY TOP DRESS DOSE FORM
T-3=INFECTED 2.64 MG/KG PYRANTEL TARTRATE DAILY COMPLETE FEED DOSE FORM
*** LESION AND ADHESION SCORE SYSTEM**
1=NORMAL 2=MILD LESION 3=MODERATE LESION 4=SEVERE LESION 5=EXTREMELY SEVERE LESION

D. Field Efficacy Studies

A total of two field efficacy studies were conducted in Alabama and Wisconsin to establish the efficacy of the daily administration of pyrantel tartrate under field conditions in preventing *S. vulgaris* larval infections and in controlling helminth infections of horses. It was determined that due to the duration of the field studies (534 days) and the extensive data collection involved that adequate data could be generated from these two studies to support approval of this new animal drug application. These same field studies, as described in the safety section, were also used as the basis for establishing the reproductive safety of pyrantel tartrate in breeding animals. Following are summaries of each study.

1. Alabama Field Study (Pivotal)

   Investigator:

   Hardin Rahe, PhD
   Auburn University
   Auburn, Alabama 36849

   A total of 64 mares and 35 foals were used in this 534 day study. Treatment groups included a non-medicated control (T-1) and a medicated group (T-2) administered pyrantel tartrate daily in a complete grain mix (1000 gm/ton) at 2.64 mg/kg body weight. Each treatment group was allowed to graze a parasite contaminated eight hectare native grass pasture. Animals were fed in groups with each mare receiving the average dose based on the average body weight for the group. Feed was placed in individual mare pans within the feeding pen. Foals were fed as a group based on the group average body weight.

   Efficacy was determined by collecting the following data: Individual animal body weights at 28 to 37 day intervals, body condition scores at each weigh period, twice daily clinical observations, daily drug intake, fecal egg and larvae culture counts at 28 to 37 day intervals throughout the study. In November of both years, six mares and six foals from each treatment group (total of 24 animals per treatment group) were euthanized for critical worm counts to assess the efficacy of the test article. Data collected at necropsy included speciated worm counts, evaluation of adhesions and arterial lesion scores due to *S. vulgaris* , arterial wall thickness, larval intimal tracks, and number of larvae recovered. The larvae were identified as small strongyles, or if of the genus Strongylus were then speciated.

   The results of this trial found in Tables 4 and 5 demonstrate that the administration of pyrantel tartrate to horses at the dose of 2.64 mg/kg body weight daily is efficacious in the prevention of *S. vulgaris* larval infection as well as being effective in controlling infections of large and small strongyles, pinworms and ascarids. There were no adverse effects of feeding the test article daily for up to 534 days on the health or performance of the mares and foals.

Table 4 Alabama Field Study Mare and Foal Necropsy Results, Two Year Data

TREATMENT	*S. VULGARIS* OBSERVATIONS - LESION** SCORE	*S. VULGARIS* OBSERVATIONS - ADHESION** SCORE	*S. VULGARIS* OBSERVATIONS - WALL THICKNESS*	*S. VULGARIS* OBSERVATIONS - NO OF TRACKS	*S. VULGARIS* OBSERVATIONS - LARVAE RECOVERED
T-1	4.14	4.14	5.52	67.43	42.86
T-1	3.9	3.3	10.89	94.9	40.2
N=	24	24	24	24	24
STD DEV	0.78	0.79	2.17	26.44	48.33
T-2	2.3	2.0	5.73	11.2	7.0
N =	24	24	24	24	24
STD DEV % **REDUCTION** T-1 VS T-2	57.1%	57.4%	47.4%	88.2%	82.6%

TREATMENT DESCRIPTION

T-1=NON-MEDICATED CONTROL

T-2=PYRANTEL TARTRATE MEDICATED 2.64 MG/KG DAILY

*** LESION AND ADHESION SCORE SYSTEM**

1=NORMAL 2=MILD LESION 3=MODERATE LESION 4=SEVERE LESION 5=EXTREMELY SEVERE LESION

**** S. VULGARIS LARVAE TRACKS IN AORTA**

PERCENT REDUCTION FOR ADHESION AND LESION SCORES: [(T-1)-1]-[(T-2)-1] ---------- [(T-1)-1]

Table 5 Alabama Field Study

Total Adult Worm and Fourth-Stage Larvae Counts for Mares and Foals, Two Year Data

Species	**Total T-1 Worm Count N=24**	**Total T-2 Worm Count N=24**	**Percent Efficacy**
A. Large Strongyles - **Adult** - *S. vulgaris*	1,590	0	100.0
A. Large Strongyles - **Adult** - *S. edentatus*	437	5	98.9
A. Large Strongyles - **Adult** - *Triodontophorus spp*	3,180	0	100.0
B. Small Strongyles - **Adult** - *Cyathostomum spp*	639,260	51,380	91.9
B. Small Strongyles - **Adult** - *Cylicocyclus spp*	728,480	13,180	98.2
B. Small Strongyles - **Adult** - *Cylicostephanus spp*	1,006,390	166,480	83.5
B. Small Strongyles - **Adult** - *Cylicodontophorus*	10,560	0	100.0
B. Small Strongyles - **Adult** - *Poteriostomum spp*	4,700	0	100.0
B. Small Strongyles - Fourth-Stage Larvae	798,200	114,424	85.7
C. Ascarids - *Parascaris equorum* - Adult	201	0	100.0
C. Ascarids - *Parascaris equorum*- Fourth-Stage larvae	397	0	100.0
D. Oxyurid - *Oxyuris equi* - Adult	16,144	3, 541	78.1
D. Oxyurid - *Oxyuris equi* - Fourth-Stage larvae	50,806	1,422	97.2

Treatment Description T-1 = non-medicated control T-2 = Pyrantel tartrate 2.64 mg/kg

2. Wisconsin Field Study (Pivotal)

   Investigator:

   Thomas J. Kennedy, PhD
   AEF Research Inc.
   Waunakee, Wisconsin 53597

   In this field study a total of fifty-six mares and thirty-nine foals were used. The study covered a period of 535 days. Treatment groups included a non-medicated control (T-1) and medicated group (T-2) administered pyrantel tartrate daily as a top-dress pellet (9600 mg/ton) at 2.64 mg/kg body weight. Each treatment group was allowed to graze a parasite contaminated ten acre native grass

pasture. Animals were individually stalled daily for administration of grain mix and medicated top-dress pellet. Mares in the control group (T-1) were dewormed twice due to the high incidence of clinical parasitism observed in the group.

Efficacy was determined by collecting the following data: Individual animal body weights at 27 to 30 day intervals, body condition scores at each weigh period, twice daily clinical observations, daily drug intake, and fecal egg and larvae culture counts at 27 to 30 day intervals throughout the study. A total of 19 mares and foals from T-1 and 22 mares and foals from T-2 were euthanized to establish the efficacy of pyrantel tartrate in controlling helminth infections and preventing *S. vulgaris* larval infections in horses. An additional five animals from T-1 and two animals from T-2 which died the first year just prior to the scheduled necropsies were also used as part of the critical worm count collections. The deaths of these additional animals were caused by conditions unrelated to the administration of pyrantel tartrate. Data collected at necropsy included speciated worm counts, measurement of adhesions and arterial lesion scores due to *S. vulgaris* , arterial wall thickness, larval intimal tracks, and number of larvae recovered. The larvae were identified as small strongyles, or if of the genus Strongylus were then speciated.

The results of this trial found in Tables 6 and 7 provide further evidence that pyrantel tartrate is effective in preventing *S. vulgaris* larval infections and in controlling infections of large and small strongyles, pinworms and ascarids in horses when administered on a daily basis at a dose of 2.64 mg/kg body weight. There were no adverse effects of feeding the test article daily for up to 535 days on the health or performance of the mares and foals.

Table 6 Wisconsin Field Study

Mare and Foal Necropsy Results, Two Year Data

TREATMENT	*S. VULGARIS* OBSERVATIONS - LESION** SCORE	*S. VULGARIS* OBSERVATIONS - ADHESION** SCORE	*S. VULGARIS* OBSERVATIONS - WALL THICKNESS* mm	*S. VULGARIS* OBSERVATIONS - NO OF TRACKS**	*S. VULGARIS* OBSERVATIONS - LARVAE RECOVERED
T-1	4.2	3.9	11.40	58.3	60.3
N =	19	19	19	19	19
STD DEV	0.76	0.85	2.59	43.26	77.30
T-2	2.7	2.4	7.32	11.5	2.4
N =	22	22	22	22	22
STD DEV	1.32	1.05	2.68	30.55	4.86
% REDUCTION T-1 VS T-2	46.7%	52.2%	36.0%	80.3%	96.0%

TREATMENT DESCRIPTION
T-1=NON-MEDICATED CONTROL
T-2=PYRANTEL TARTRATE MEDICATED 2.64 MG/KG DAILY
*** LESION AND ADHESION SCORE SYSTEM**
1=NORMAL 2=MILD LESION 3=MODERATE LESION 4=SEVERE LESION 5=EXTREMELY SEVERE LESION
**** S. VULGARIS LARVAE TRACKS IN AORTA** PERCENT REDUCTION FOR ADHESION AND LESION SCORES [(T-1)-1]-[(T-2-1] ---------- [(T-1)-1]

Table 7 Wisconsin Field Study

Total Adult Worm and Fourth-Stage Larvae Counts for Mares and Foals, Two Year Data

Species	Total T-1 Worm Count N=24	Total T-2 Worm Count N=24	Percent Efficacy
A. Large Strongyles - Adult - *S. vulgaris*	252	0	100.0
A. Large Strongyles - Adult - *S. edentates*	43	0	100.0
A. Large Strongyles - Adult - *Triodontophorus spp*	2,760	0	100.0
B. Small Strongyles - Adult - *Cyathostomum spp*	293,373	40	99.9
B. Small Strongyles - Adult - *Cylicocyclus spp*	284,006	282	99.9
B. Small Strongyles - Adult - *Cylicostephanus spp*	344,092	1,080	99.7
B. Small Strongyles - Adult - *Cylicodontophorus*	480	0	100.0
B. Small Strongyles - Adult - *Poteriostomum spp*	1,600	0	100.0
B. Small Strongyles - Fourth-Stage Larvae	201,082	380	99.8
C. Ascarids - *Parascaris equorum* - Adult	1,297	0	100.0
C. Ascarids - *Parascaris equorum*- Fourth-Stage larvae	3,990	0	100.0
D. Oxyurid - *Oxyuris equi* - Adult	39,220	240	99.4
D. Oxyurid - *Oxyuris equi* - Fourth-Stage larvae	127,261	2,280	97.8

Treatment Description
T-1 = Non-medicated control
T-2 = Pyrantel tartrate 2.64 mg/kg

III. TARGET ANIMAL SAFETY

A. Long Term Target Animal Safety Study

(Pivotal) Investigator:

Diane J. Fagerberg, PhD
Colorado Animal Research Ent. Inc.
Fort Collins, Colorado

This study was conducted to gather data on the long term safety of pyrantel tartrate when administered orally via feed to horses at ten times the anticipated field use level. A dosing regimen of 26.4 mg/kg body weight per day was conducted for 196 consecutive days.

Twelve yearling horses (6 geldings and 6 mares) were provided the 10X dosage of pyrantel tartrate for 196 consecutive days as an admixed additive to their daily grain mixture. Horses were stalled daily only for grain feeding and otherwise were pasture grazed with supplemental long stem hay and *ad libitum* water. The test animals were Quarter Horse, Appaloosa, Thoroughbred and mixed breed. All test animals were placed on the same treatment regimen. A 30 day pretrial period of three data collections (days -30, -7 and -1) provided baseline data for comparison to treatment period data.

Test article effect was monitored by collecting the following data; twice daily clinical scores, daily feed and drug intake; and 28 day interval body weights, body condition scores, complete physical examinations, fecal examinations, blood and serum chemistries and hematology. On day 196, three randomly predesignated horses were necropsied and their tissues examined microscopically.

Data from the study were evaluated clinically and statistically. There were no findings that suggested an adverse effect from the 10X, long term dosage of pyrantel tartrate when in-life data from the twelve treated horses were compared to normal values and their respective pretrial baseline values; and when tissues of three necropsied animals were grossly and histopathologically evaluated.

B. Foal Target Animal Safety Study (Pivotal)

Investigator:

Diane J. Fagerberg, PhD
Colorado Animal Research Ent. Inc.
Fort Collins, Colorado

This study was designed to assess the safety of pyrantel tartrate in young foals. Three treatment groups received either 0X, 5X, (13.2 mg/kg) or 10X (26.4 mg/kg) the recommended oral dose of 2.64 mg/kg body weight/day for 84 to 98 days. Each treatment group was comprised of four male and six female foals that ranged between one and three months of age at study initiation.

The foals were co-housed with, and continued to suckle, their parent mares for the duration of the acclimation and treatment periods. The acclimation period encompassed 30 days during which baseline data were collected. Parameters measured in this study included body weights, clinical observations, physical examinations, and blood and fecal clinical pathology evaluations at specific study intervals.

There were no distinct biological or statistically significant indications of treatment effects in the hematology or serum chemistry parameters. Hematology values were in general agreement with published values for normal ranges. There were two overall trends in hematology values, independent of treatment group: 1) a decline of approximately 14% in total blood cell count and 2) an upward trend of approximately 25% in total white blood cell counts. These changes were considered normal consequences of foal maturation and not indicative of any blood disorder.

Overall treatment period serum uric acid values were significantly higher for foals treated at the 10X level versus the untreated controls, but actual values for this group were still within the range of normal published values. The only general trends, irrespective of treatment group, emerging over the duration of the

acclimation and study periods were a slight increase in blood urea nitrogen (BUN) and decreasing serum glutamic pyruvic transaminase (SGPT) levels as the foals became older. These values were still within the range of normal published values and the change was considered a function of foal maturation.

The results of the physical examinations, clinical observations and fecal examinations failed to reveal any deleterious effects on the health of the foals from feeding pyrantel tartrate at a level up to 10X the recommended dose. The results of this study further substantiate the safety of this product in horses when administered on a continuous basis.

C. Drug Tolerance Study (Pivotal)

Investigator:

R.M. Bodden
Hazleton Laboratories America, Inc.
Madison, Wisconsin 53604

This study was conducted to demonstrate that the administration of up to 25 times the use level of pyrantel tartrate in horses would not cause any adverse effects. A total of ten yearling horses (four gelding and six females) were given pyrantel tartrate at a rate of 66 mg/kg of body weight for 5 consecutive days (25 times the recommended dose). The test material was administered by mixing a measured amount into each animals daily grain mix ration. The effect of the treatment was measured by feed consumption, water consumption, body weight, physical examinations and clinical observations. Blood was collected for hematology and clinical chemistry tests on days -32, -11, -1, 1, 2, 3, 4 and 5.

A transient increase in the WBC count of both sexes was observed on Day 3 and in females only on Day 4 which was characterized by an increase in the absolute neutrophil count. While mean values for the counts were mildly to moderately higher than reference limits, they approximate values obtained from the same horses on day -32. In the absence of physical evidence of inflammatory disease and considering that the counts soon returned to levels similar to day -1, these changes were not considered to be caused by the test material.

Statistically significant differences observed in mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and prothrombin time were inconsistent between sexes and over time and represented very small changes. Furthermore, there were no changes in other erythrocyte variables that would suggest a treatment related effect on red blood cells.

Glucose was transiently increased on Days 1, 2 and 3 in both sexes. On Day 2 the increase was almost 50% above the baseline values. On Day 5, the glucose values were similar to the Day -1 values. It is believed the addition of molasses to the diet on Days 1 through 4 may have contributed to this increase in glucose. When molasses was not fed to the horses on Day 5, the glucose values were not increased. Other differences seen in the clinical pathology variables were considered to be the result of normal biological variation, not related to pyrantel tartrate and not toxicologically meaningful. The differences represented small changes that were inconsistent, frequently present before Day -1, and of no pathological significance.

There were no adverse effects found during the routine clinical observations and physical examinations that were considered related to the feeding of pyrantel tartrate. The results of this study found that no adverse effects were produced in yearling horses when pyrantel tartrate was fed for five consecutive days at a level of 66 mg/kg of body weight (25 times recommended dose).

D. Reproductive Safety Studies (Pivotal)

Two studies were conducted to evaluate the safety of pyrantel tartrate on the reproductive performance of mares and stallions when administered daily at 2.64 mg/kg of body weight. These studies are the same as the field efficacy studies described earlier in the FOI Summary. Because these studies were conducted in conjunction with the field studies in Alabama and Wisconsin, the mares were administered the test drug at 2.64 mg/kg body weight instead of some multiple of the recommended dose. Following are the details of the studies:

A total of 120 mares and nine stallions were used in the two studies to determine the safety of the test article on reproduction. All of the medicated mares were fed the test article for at least 500 consecutive days and in some cases for over 700 days (two complete breeding cycles). This duration of administration is several times the probable duration of use for a single course of treatment and subjects the test article to a strenuous test of its safety. In both studies the test article was administered during each of the three trimesters of gestation as well as during lactation and breeding seasons without adverse effects in the mares and stallions or their foals when compared to the control animals. The design and duration of these studies were determined adequate to establish the reproduction safety of pyrantel tartrate.

1. Study Number 6250A-83-004 Reproductive Safety

   Investigator:

   Hardin Rahe, PhD
   Auburn University
   Auburn, Alabama 36849

   A total of sixty-four mares and four stallions were used in this study to evaluate the reproductive safety in horses of the daily administration of pyrantel tartrate. The study was conducted over two breeding seasons for a total of 534 days. Treatment groups included a non-medicated control and a medicated group administered pyrantel tartrate daily in a complete grain mix (1000 gm/ton) at 2.64 mg/kg body weight. Mares in each treatment group were allowed to graze a parasite contaminated eight hectare native grass pasture. Animals were fed in groups with each mare receiving the average dose based on the average body weight for the group. Feed was placed in individual mare pens within the feeding pen.

   Mares were bred by either hand-mating or artificial insemination in each of the two breeding seasons. Each mare that was bred by artificial insemination received a minimum of 500 million live, normal sperm per breeding. Uterine biopsies were performed on mares that did not conceive at the first breeding. Pregnancy determination was accomplished by either palpation, ultrasound, plasma progesterone or a combination of the procedures. Semen was evaluated prior to each breeding.

The parameters measured in the assessment of reproductive safety included: Individual animal body weights at 28 to 37 day intervals, body condition scores at each weigh period, twice daily clinical observations, daily drug intake, number of mares cycling, number bred, percent conception, foaling data which included type of delivery, condition at birth and early growth rate. Stallion semen was evaluated for motility, morphology, concentration and volume.

The administration of pyrantel tartrate to mares at the dose of 2.64 mg/kg body weight daily did not adversely effect the reproductive performance as determined by percent cycling, percent bred, percent conception of mares bred and pregnancy rates at the conclusion of the study. The first breeding season conception rates were 50.0 and 72.7 percent for control and medicated groups respectively. Conception rates in the second year were 94.4 percent for each treatment group. There was no adverse effect on stallion reproductive efficacy as determined by semen characteristics and conception rates. There were no adverse effects of feeding the test article daily on the health or performance of mares, stallions or foals.

In order to obtain additional data on foaling and early growth rate of foals, 23 of the original mares that were determined to be pregnant were selected to remain on drug until 30 days after foaling (approximately and additional 190 days). Eleven of the mares in this group were on medication for a total of 724 days at the termination of the study. Twenty one of the 23 mares delivered a normal healthy foal. The administration of pyrantel tartrate daily at 2.64 mg/kg body weight had no apparent adverse effect on parturition or early growth rate of foals.

2. Study Number 6250A-83-003 Reproductive Safety

Investigator:

Thomas J. Kennedy, PhD
AEF Research Inc.
Waunakee, Wisconsin 53597

In this study a total of fifty-six mares and five stallions were used. The study was conducted over a period of 535 days. Treatment groups included a non-medicated control (T-1) and a medicated group (T-2) administered pyrantel tartrate daily as a top dress pellet (9600 gm/ton) at 2.64 mg/kg body weight. Mares in each treatment group were allowed to graze a parasite contaminated ten acre native grass pasture. Animals were individually stalled for daily administration of grain mix and medicated top dress pellet. Mares in the control group (T-1) were dewormed twice due to the high incidence of clinical parasitism observed in the group.

Estrus cycles of mares in both treatment groups were synchronized with injectable prostaglandin during each of the two breeding seasons. Mares were bred by either hand-mating or artificial insemination. Each mare that was bred by artificial insemination received a minimum of 100 million live, normal sperm per breeding. Pregnancy determination was accomplished by either palpation, serum PMSG or ultrasound readings. Semen was evaluated prior to each breeding.

The parameters measured in the assessment of reproductive safety included individual animal body weights at 27 to 30 day intervals, body condition scores at each weigh period, twice daily clinical observations, daily drug intake, number of mares cycling, number bred, percent conception, foaling data which included type of delivery, condition at birth and early growth rate. Stallion semen was evaluated for motility, morphology, concentration and volume.

The administration of pyrantel tartrate to mares at the dose of 2.64 mg/kg body weight daily did not adversely effect the reproductive performance as determined by percent cycling, percent bred, percent conception of mares bred and pregnancy rates at the conclusion of the study. Over the two years the conception rates were 36% and 50% for the control and medicated groups, respectively. The conception rates were negatively impacted the first year due to breeding too late in the season, mares in poor body condition and the mares being subjected to elevated environmental temperatures during early gestation. The conception rates between the control and medicated groups were both years of the study with an increased conception rate seen in the medicated group both years. There was no adverse effect on stallion reproductive efficacy as determined by semen characteristics and conception rates. Moreover, percent mares foaling and foal performance was not adversely affected by the consumption of the test article.

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is approved for use only in horses that are not to be used for food and is to be labeled:

WARNING: Not for use in horses intended for food.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that pyrantel tartrate is safe and effective when used in accordance with the label directions against the following parasites: For the prevention of *Strongylus vulgaris* larval infection in horses.

For control of the following parasites in horses:

- LARGE STRONGYLES (adults) *S. vulgaris*, *S. edentatus*, *Triodontophorus* spp.
- SMALL STRONGYLES (adult and fourth-stage larvae) *Cyathostomum* spp. *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp., *Poteriostomum* spp.,
- PINWORMS (adult and fourth-stage larvae) *Oxyuris equi*
- ASCARIDS (adult and fourth-stage larvae) *Parascaris equorum*.

This product is approved for OTC (over the counter) use as a Type B medicated feed or top dress in a horses daily ration. The chances of overdosing are minimal, since the labeling provides adequate directions for safe use by the laity. The drug is effective against all the common helminths of economic importance in the equine, therefore, a specific diagnosis is not mandatory for proper use of the medicated feed or top dress. The parasite of most economic importance among the parasites listed on the label is *Strongylus vulgaris*, especially its migratory larvae. If not treated the migratory larvae

can cause verminous arteritis which can result in the death of animal. Strongid 48 prevents strongyle larval migration.

VI. LABELING

1. Front panel package label Strongid 48
2. Back panel package label Strongid 48
3. Package insert
4. Placard bulk product

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.