Approval Date: November 18, 2003

FREEDOM OF INFORMATION SUMMARY

NADA 141-178

NAVIGATOR
(32% nitazoxanide)
Antiprotozoal Oral Paste

"…for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona.*"

Sponsored by:

IDEXX Pharmaceuticals, Inc.
Greensboro, NC 27410

TABLE OF CONTENTS

1. GENERAL INFORMATION:

a. File Number: NADA 141-178

b. Sponsor: IDEXX Pharmaceuticals, Inc.
4249-105 Piedmont Pkwy
Greensboro, NC 27410

Drug Labeler Code: 065274

c. Established Name: nitazoxanide

d. Proprietary Name: NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste

e. Dosage Form: Oral Paste

f. How Supplied: NAVIGATOR Antiprotozoal Oral Paste is supplied in a plastic oral-dose syringe which contains 85 grams of paste. Each gram of paste contains 320 mg of nitazoxanide (32% w/w). Syringes are fitted with a dosage ring designed to deliver 22.72 mg of nitazoxanide/lb, and are marked for a horse weighing up to 1,200 pounds. The NAVIGATOR Antiprotozoal Oral Paste dispensing box contains 26 syringes which provide sufficient paste to treat one 1,200 pound horse for 28 days (5 days at 11.36 mg/lb and 23 days at 22.72 mg/lb).

g. How Dispensed: Rx

h. Amount of Active Ingredients: Each syringe contains 27.2 g of nitazoxanide

i. Route of Administration: Oral

j. Species: Equine

k. Recommended dosage: Always provide the Client Information Sheet to the animal owner or person treating the horse with each prescription. NAVIGATOR Antiprotozoal Oral Paste should be administered orally once a day for 28 days as follows:

Days of Administration	Target Dose
Days 1-5	11.36 mg/lb body weight
Days 6-28	22.72 mg/lb body weight

NOTE: A total of 26 syringes are included in the NAVIGATOR Antiprotozoal Oral Paste dispensing box. The

three syringes in the first three spaces will be used to dose the horse for days 1-5. The remaining 23 syringes will dose the horse for days 6-28. The dose is 11.36 mg/lb for the first five (5) days, and 22.72 mg/lb for days 6-28.

Nitazoxanide has not been evaluated in horses that weigh more than 1,200 pounds.

l. Pharmacological Category: Antiprotozoal

m. Indications: NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste in indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

2. EFFECTIVENESS:

a. Dosage Characterization:

Starting Dose: The 11.36 mg/lb dose is used for days 1-5 to allow for a slower kill of the protozoal microorganisms and allow the horse time to accommodate to any change that may occur in the intestinal flora. Starting the horse at a dose of 22.72 mg/lb may produce a "treatment crisis," which is a worsening of neurological signs, elevated body temperature, decreased appetite and lethargy, presumably due to the rapid kill of protozoal microorganisms.

Pharmacokinetics: Eight (4 males, 4 females) mixed-breed, healthy horses received either a single dose or multiple doses of NAVIGATOR Antiprotozoal Oral Paste formulation for seven consecutive days. Nitazoxanide is rapidly metabolized to the active metabolite, deacetylnitazoxanide. Plasma drug levels of deacetylnitazoxanide were non-detectable by 24 hours post-dosing. According to a validated method, the limit of detection (LOD) was estimated to be 0.015 ppm and the lower limit of quantification (LOQ) was 0.02 ppm. The data from the pharmacokinetic study are presented in the following table:

Table 1. Pharmacokinetic Parameters Determined by Single and Multiple Doses (7) of NAVIGATOR Antiprotozoal Oral Paste in Healthy Horses (mean ± SD, N=8)

Dose (22.72 mg/lb)	C_{max} (ppm)	T_{max} (hrs)	$AUC_{0\text{-}LOQ}$ (ppm•hrs)
Single	0.51 ± 0.30	2.13 ± 1.13	1.913 ± 0.53
Multiple	0.97 ± 0.49	3.250 ± 3.57	4.770 ± 2.78

C_{max} (Maximum concentration of deacetylnitazoxanide achieved)
T_{max} (Time maximum concentration was achieved)
$AUC_{0\text{-}LOQ}$ (Area Under the Curve from time 0 through the last sample with deacetylnitazoxanide concentration above the LOQ)

Based on the C_{MAX} and AUC values of the single and multiple doses, some accumulation occurs. When comparing the individual pharmacokinetic data (C_{max},T_{max}, AUC) across the study days and based on the mean standard deviations for each value, there was intersubject variability in the rate and extent of product disposition.

Cell Culture Data: Experiments conducted in cell culture[1] showed that dosages of 1.0 ppm or greater prevented measurable monolayer destruction in a lesion based microassay against developing *Sarcocystis neurona* merozoites (SN-3 strain). In this assay, the concentration of nitazoxanide that inhibited the merozoites by 50% (inhibitory concentration 50; IC_{50}) was 0.52 ppm.

Conclusion: The C_{max} for deacetylnitazoxanide after multiple doses of the 22.72 mg/lb dose was 0.97 ppm (1.9X the IC_{50} of 0.52 ppm). These data predict that the concentrations of deacetylnitazoxanide in the plasma would reach therapeutic levels against *S. neurona* over the 28-day dosing period. The 28-day course of therapy was selected based on the pharmacokinetics of the drug and the life cycle of the organism. The merozoites develop in a 10-14 day period after ingestion of the oocysts. The 28-day course of therapy is roughly twice the length of this life cycle to help ensure that the protozoal organism is controlled before therapy is discontinued.

[1] Lindsay, D.S., Zhang, Y., Dubey, J.P., et al. Determination of the activity of nitazoxanide against *Sarcocystis neurona* in cell cultures, in Proceedings of the American Association of Veterinary Parasitology 43rd Annual Meeting, 1998:44.

b. Substantial Evidence:

(1) Historical Control:

EPM is usually a progressive neurological disease. It has been estimated that up to 55-65%[2] of horses respond favorably to treatment. However, it is further estimated that no more than 10% of treated horses recover completely. One of the most important points to consider is that EPM produces highly variable clinical disease. Historical controls were used in the field studies because, without treatment EPM is usually a progressive disease. At the time these studies were conducted, there was no FDA approved treatment for EPM. The use of historical controls in the evaluation of compounds for effectiveness is described in 21 CFR 514.117(b)(4)(iv).

(2) Field Study I:

This field study was conducted at thirteen sites, geographically distributed across the United States.

(a) Participating Investigators:

Robert Buell, DVM Hialeah, FL	G. David McCarroll, DVM Goldsby, OK
Gary Doxtater, DVM Williamsburg, VA	Dawn Mrad, DVM Wentzville, MO
Diane Finch, DVM Ft. Wayne, IN	Thomas Schwerbrock, DVM Kewanee, IL
Karen Flipse, DVM Vass, NC	Bruce Sickels, DVM Union City, IN
L. Mark Haugland, DVM Conroe, TX	Nicholas Vatistas, BVSc, PhD, MRCVS Vacaville, CA
Richard Henninger, DVM Findlay, OH	Wesley Williams, DVM Irving, TX

[2] Granstrom DE. *Understanding Equine Protozoal Myeloencephalitis*:Your Guide to Horse Health Care and Management. Lexington: The Blood-Horse Inc, 1997:10.

Michael Major, DVM
Edmond, OK

(b) Study Design: NAVIGATOR Antiprotozoal Oral Paste was administered once a day for five days at 11.36 mg/lb and then once a day for 23 days at 22.72 mg/lb. The effectiveness of NAVIGATOR Antiprotozoal Oral Paste for treating EPM was evaluated by a standardized neurological examination and Western blot (WB) assay of the cerebral spinal fluid (CSF). All investigators were trained to conduct a standardized neurological examination using sample cases that had been videotaped by the sponsor.

(c) Variables Evaluated: Investigators performed the neurological examination on each horse prior to initiation of dosing (Day 0), on Day 28 (last day of dosing) and Day 85 (57 days post dosing). The Day 85 evaluation was the critical endpoint. After performing the neurological examination, the investigator assigned a grade or fraction of a grade to each horse based on the modified Mayhew scale:

0 = no gait deficits,
1 = deficits barely perceptible, worsened with head elevation,
2 = deficits noted at a walk,
3 = deficits noted at rest and walking; nearly falls with head elevation,
4 = falls or nearly falls at normal gait,
5 = recumbent patient.

In order to be considered a success by the investigator, a horse had to improve at least one grade on the modified Mayhew scale by Day 85 and/or have a negative result from a Western blot assay of the CSF by Day 85.

The neurological examination was also videotaped (Day 0, Day 28, Day 85) for each horse. A separate videotape was used for each neurological examination on a horse. In order to accomplish objectivity and corroborate the investigator's evaluation, three independent equine experts reviewed and graded each videotape. The experts were masked to the date and the identification of the horse while reviewing each tape. If two or more of the three experts indicated that the horse improved any amount, then the case was considered a "corroborated" success.

All horses entered the study with a positive CSF Western blot assay for *S. neurona* and with grade 2 to 4 asymmetric spinal ataxia or grade 1 spinal ataxia if accompanied by muscle atrophy or cranial nerve deficits.

NAVIGATOR Antiprotozoal Oral Paste was used concomitantly with other medications including anthelmintics, antibiotics, non-steroidal and steroidal anti-inflammatory agents, diuretics, tranquilizers and vaccines.

(d) Results: Ninety-six (96) horses were enrolled into the study and 47 were excluded from the analysis of effectiveness for various reasons. Forty-nine (49) horses were included in the analysis. The following tables describe the patient population:

Table 2. Study Population by Age

Age	Number (%)
1 - 5 years	18 (37%)
>5 – 10 years	16 (33%)
>10 - 15 years	8 (16%)
>15 - 20 years	5 (10%)
>20 - 25 years	2 (4%)
Total	49 (100%)

Table 3. Study Population by Sex

Sex	Number (%)
Stallion	3 (6%)
Gelding	25 (51%)
Mare	21 (43%)
Total	49 (100%)

Table 4. Study Population by Breed

Breed	Number (%)
Arabian	1 (2%)
Hanoverian	2 (4%)
Missouri Fox Trotter	1 (2%)
Paint	4 (8%)
Paso Fino	1 (2%)
Peruvian Paso	1 (2%)
Quarter Horse	14 (29%)
Quarter Horse X	3 (6%)
Standardbred	2 (4%)
Thoroughbred	14 (29%)
Thoroughbred X	3 (6%)
Warmblood	2 (4%)
Westphalian	1 (2%)
Total	49 (100%)

Based on the investigators' clinical evaluations and the results of the CSF analyses, 28/49 (57%) of the cases were considered "successes." Seven of the 49 horses (14%), had a negative result from a Western blot assay of the CSF collected on Day 85. Three of the 49 horses (6%) treated with NAVIGATOR Paste in the study achieved Grade 0 (clinically normal) at Day 85.

In order to corroborate the cases deemed successful by the clinical investigator, equine experts reviewed the videotapes of the success cases in a masked fashion. A horse whose CSF Western Blot converted to negative, was deemed a success and was not reviewed by the experts. Based on the corroboration of the experts' scores, 22 of 49 horses (45%) had an improved neurological examination on Day 85 and/or a negative result from a Western blot assay of the CSF collected on Day 85. Seven of the 22 horses (32%) evaluated as successes had a negative result from a Western blot assay of the CSF collected on Day 85.

Results of the effectiveness scores from the clinical investigators and corroboration by the equine experts are shown below:

Table 5. Effectiveness Results from the Clinical Investigators and Equine Experts in Field Study I.

	Number of Successes	Percent
Cases rated as Successes by Investigators	28/49	57.1%
-Cases not corroborated by experts	-6	
Total Number of Corroborated Successes	22/49	44.9%

Adverse reactions were observed in this field study and are described in Section 3 of this FOI Summary.

Based on the investigators' clinical evaluations and the results of the CSF analyses, 28/49 (57%) of the cases were considered "successes." Seven of the 49 horses (14%), had a negative result from a Western blot assay of the CSF collected on Day 85. Three of the 49 horses (6%) treated with NAVIGATOR Antiprotozoal Oral Paste in the study achieved Grade 0 (clinically normal) at Day 85.

Twenty-two of 49 horses (45%) had improved neurological examinations on Day 85 and/or a negative result from a Western blot assay of the CSF collected on Day 85. Seven of the 22 horses (32%) evaluated as successes had a negative result from a Western blot assay of the CSF collected on Day 85.

Adverse reactions were observed in this field study and are described in Section

3 (Target Animal Safety) of this FOI Summary.

(3) Field Study II:

(a) Study Design: This study was designed to obtain additional effectiveness and safety data. Basic information was collected about the response to therapy. CSF collection and analysis were not requirements of this study. Four-hundred-nineteen (419) horses from 150 clinical investigators were enrolled in the study. Two hundred fifty horses completed the study and provided complete results of the treatment. The protocol consisted of documenting the diagnosis of EPM, treating with nitazoxanide and documenting the neurological abnormalities. Investigators were not required to videotape the neurological examinations.

For 46 horses (18%), treatment was administered once a day for 28 days using a dose of 22.72 mg/lb for the entire treatment period. For 204 horses (82%), treatment was comprised of a graduated dose of 11.36 mg/lb once a day for five or six days, followed by a dose of 22.72 mg/lb once a day for 22 or 23 days.

(b) Variables Evaluated: Investigators performed the neurological examination on each horse prior to initiation of dosing (Day 0), and approximately 85 days after beginning nitazoxanide therapy. CSF was obtained whenever possible. Many owners and veterinarians declined to collect the post-treatment CSF sample in view of the magnitude of the horses' neurological improvement and the inherent risks associated with the collection procedure.

(c) Results: Nitazoxanide administration was interrupted in 24 cases during this field study (58% of these cases were reported by one investigator). Five of these cases were treated with 22.72 mg/lb beginning on day 1 and the remaining 19 cases received nitazoxanide according to the graduated dosage regimen. An elevated body temperature was observed in each instance. Interruption of nitazoxanide administration occurred within the first nine days in 75% of these cases, and the median duration that a horse did not receive nitazoxanide was two days. In two cases, nitazoxanide administration was interrupted again on treatment days 15 and 22, respectively.

Success was based upon the same criteria used for the investigators in the first field study, i.e., one full grade improvement on neurological examination and/or a negative CSF-WB on study Day 85. Of the horses that completed the study, eighty-one percent (81%) were considered successes.

Table 6. Effectiveness Results from the Investigators in Field Study II

	N = cases	Percent
Complete Cases	250	
Success	203	81%
Failure	47	19%
Incomplete Cases	169	
Total Cases	419	

One hundred-fifteen (115) of the 250 horses had been previously treated for EPM with other therapies. Seventy-eight percent (90/115) of these were successfully treated with nitazoxanide.

Thirty-eight of the 188 (20%) receiving follow-up spinal centesis had a negative result from the Western blot assay of the CSF. Forty-seven (19%) of the 250 horses completing the study, were considered failures.

Adverse reactions were observed in this field study and are described in Section 3 of this FOI Summary.

(4) Conclusions of field effectiveness studies:

In the field studies, 299 horses completed the 28 day treatment. Clinical effectiveness based upon a negative CSF tap or improvement in the neurological condition of the horse was 57% in Field Study I and 81% in Field Study II.

Adverse reactions did occur in these studies and are discussed in Section 3 (Target Animal Safety) of this FOI Summary.

3. TARGET ANIMAL SAFETY:

a. Tolerance Study:

(1) Type of Study: Tolerance Study

(2) Study Director: John W. Campbell, Ph.D.
Southwest Bio-Labs, Inc.
Las Cruces, NM

(3) General Design:

(a) Compliance: This study was conducted in compliance with the FDA Good Laboratory Practice Standards, 21 CFR 58.

(b) Purpose: The purpose of this study was to define the toxic signs associated with a single administration of an elevated dose of nitazoxanide.

(c) Test Animal Allocation and Drug Administration: Eight horses were given one dose of 113.64 mg/lb (which is 10X the starting dose of 11.36 mg/lb or 5X the regular dose of 22.72 mg/lb) and observed for 14 days.

(4) Results:

(a) Clinical Findings: Transient depressed appetite, loose stools and lethargy were observed, and lasted from 11 to 14 days post-treatment. One horse developed edema in the legs and received supportive therapy (flunixin meglumine for one day, kaolin pectin for three days) beginning eight days after treatment. No other supportive therapy was administered. All eight horses returned to normal.

(b) Pathology: Necropsy was not performed.

(5) Conclusion: The results of this study indicate that a single 113.64 mg/lb dose of NAVIGATOR Antiprotozoal Oral Paste resulted in reversible signs consisting of a depressed appetite, loose stools and lethargy in all eight horses. One of these eight horses required treatment for edema in the legs.

b. Toxicity Study I:

(1) Type of Study: Toxicity Study

(2) Study Director: John W. Campbell, Ph.D.
Southwest Bio-Labs, Inc.
Las Cruces, NM

(3) General Design:

(a) Compliance: This study was conducted in compliance with the FDA Good Laboratory Practice Standards, 21 CFR 58.

(b) Purpose: The purpose of this study was to define the safety margin of the product at various dosages.

(c) Test Animal Allocation and Drug Administration:

Table 7. Dosage Rate in NAVIGATOR Antiprotozoal Oral Paste Toxicity Study I

Group (4M, 4F)	Duration	Daily Dosage	Average Group Dosage Rate
1	60 DAYS	Placebo (sham dosed)	0
2	60 DAYS	1 syringe NAVIGATOR	28.18 mg/lb
3	60 DAYS	2 syringes NAVIGATOR	57.27 mg/lb
4	4 DAYS	4 syringes NAVIGATOR	110.91 mg/lb
5	7 DAYS 7 DAYS 60 DAYS	1 syringe NAVIGATOR 2 syringes NAVIGATOR 3 syringes NAVIGATOR	28.18 mg/lb 57.27 mg/lb 78.18 mg/lb

All horses were observed for seven days after the last treatment. There were eight horses per group.

(4) Results:

(a) Clinical Findings:

1 In Group 1 (Placebo), none of the eight horses experienced any adverse clinical signs.

2 In Group 2 (28.18 mg/lb, 1.2X regular dose), all eight horses completed the study. Three horses showed no adverse reactions during the study period. Four of the horses developed a mild, transient, depressed appetite between Days 4 and 15 of the study. Three of the horses became lethargic at some time between Days 4 and 8 of the study. Two of the Group 2 horses voided loose stools periodically between Days 6 and 36 of the study. All eight horses in Group 2 recovered without therapeutic intervention.

3 In Group 3 (57.27 mg/lb, 2.5X regular dose), six horses completed the study. Seven of the horses developed a mild, depressed appetite periodically during the study period, beginning on Day 4. All eight horses were occasionally lethargic during the study, beginning on Day 3. Four of the Group 3 horses voided loose stools periodically during the study period beginning on Days 4 through 64. Two of the horses in Group 3 developed severe clinical signs and died after being dosed for 15 days and 37 days, respectively. The cause of death for both horses was severe erosion and ulceration of the colon. Two horses received supportive therapy after nitazoxanide treatment ended (lactated Ringers solution for 6-10 days, kaolin pectin for 0-7 days, a potentiated

sulfonamide for 0-3 days, and flunixin meglumine for 0-2 days) and one died. The remaining horses survived without therapeutic intervention.

4 In Group 4 (110.91 mg/lb, 4.9X regular dose), dosing was discontinued on Day 4 because horses in this treatment group developed severe clinical signs (anorexia, diarrhea and lethargy). All eight horses developed decreased appetite and became lethargic during the first three days of the study. Four of the horses voided loose stools for one day each, during Days 2-5 of the study. Five of the eight horses given the 110.91 mg/lb average daily dose died within the first two to four days of the study. The cause of death in all cases was severe erosion and ulceration of the colon. The three remaining horses recovered after removal from the study on Day 4 and administration of supportive therapy for six days (lactated Ringers, carafate, kaolin pectin). They also received a 12-day course of a potentiated sulfonamide.

5 In Group 5, horses were dosed with the contents of one syringe per day for one week, two syringes per day for a second week and then three syringes per day for an additional 60 days (average maximum dose 78.18 mg/lb, 3.4X regular dose). All eight horses developed decreased appetite and were periodically lethargic, beginning as early as Day 4. Four horses periodically voided loose feces beginning on Days 9-23. Five horses successfully completed this dosage regimen without therapeutic intervention. Three horses demonstrated clinical signs of drug toxicity and were removed from the study on Days 17 through 31. They developed significant weight loss, anorexia, lethargy, and decreased gut sounds. These three horses recovered with supportive therapy (lactated Ringers solution, kaolin pectin, and potentiated sulfonamide). Twenty-three days later, one horse developed gastroenteritis complicated by Salmonellosis and died.

(b) Clinical Pathology: During this study there were numerous findings of elevated or depressed cellular elements in the hemogram. Similarly, erratic changes in clinical chemistry were observed, but no dose response was established. Although statistical analysis failed to demonstrate a dose response, some of the findings were present in horses that were affected by severe gastrointestinal illness, and thus are indirectly related to nitazoxanide toxicity. Hypoproteinemia was occasionally observed in horses in the higher dosage groups and was likely associated with a protein losing enteropathy. Several hemograms demonstrated a stress leukogram, which is consistent with the degree of toxicity observed in this study.

(c) Post-mortem Pathology: Gross and histopathological examination of animals that died on the study indicates the colon as the target tissue. In animals with

severe colonic lesions (ulcerations, erosions), the stomach, small intestine and cecum were also affected; but to a lesser degree. No treatment-related effects on other tissues were noted in study animals.

(5) Conclusions: This study demonstrated that administration of one entire syringe of NAVIGATOR Antiprotozoal Oral Paste (average dose of 28.18 mg/lb) resulted in signs of toxicity consisting of a mild, depressed appetite, lethargy and loose feces. When two syringes were administered, the same toxicity was noted and in addition, two horses died due to severe erosion and ulceration of the colon. Doses exceeding two syringes/horse/day were not tolerated.

c. Toxicity Study II:

(1) Type of Study: Toxicity Study

(2) Study Director: Wendy K. Rowland, MS
Johnson Research, LLC
Parma, ID

(3) General Design:

(a) Compliance: This study was conducted in compliance with the FDA Good Laboratory Practice Standards, 21 CFR 58.

(b) Purpose: The purpose of this study was to clearly define the safety of the product at the recommended dosage.

(c) Test Animal Allocation and Drug Administration:

Table 8. Dosage Rate in NAVIGATOR Antiprotozoal Oral Paste Toxicity Study II

Group(4M, 4F)	Duration	Daily Dosage	Group Description
1	28 DAYS	sham dosed	Placebo
2	28 DAYS	11.36 mg/lb days 1-5, 22.72 mg/lb days 6-28	1X Group
3	28 DAYS	22.72 mg/lb days 1-5, 45.45 mg/lb days 6-28	2X Group

All horses were observed for seven days after the last treatment. There were eight horses in each treatment group.

(4) Results:

(a) Clinical Findings: All horses in all groups completed the dosing portion of the study.

1 In Group 1 (Placebo), four of the horses showed decreased appetite on at least one day of the study. Three horses voided loose stools or had limb or ventral edema on at least one day of the study. Two horses voided discolored brown (normal color was green) feces. Four horses produced malodorous feces during the study. Four horses had no clinical findings during the study. One horse lost weight, but the group gained an average of 43 pounds during the study.

2 In Group 2 (1X group), one of the horses showed decreased appetite and had limb edema occasionally during the study. Three horses voided loose feces on at least one day of the study. Two horses voided discolored brown feces. Two other horses produced malodorous feces during the study. Four horses had no clinical findings during the study. No horses lost weight, and the group gained an average of 61 pounds during the study. These horses gained more weight during the study than any other group.

3 In Group 3 (2X group), eight horses had decreased appetite during the study period. Five horses became lethargic during the study. All eight horses had loose and malodorous feces on at least one day during the study period. Four horses had discolored brown or black feces. Five horses developed limb or ventral edema during the study. Three horses in Group 3 developed fever for at least one day during the study period. One was treated with hydrotherapy for three days and another horse was given five days of oral electrolytes. One horse in Group 3 developed enterocolitis near the end of the study period and was given supportive therapy including antibiotics, flunixin meglumine, kaolin pectin, IV fluids, omeprazole and carafate. It was euthanized at the end of the study. Diagnostic testing, complete necropsy and histopathology revealed findings consistent with alteration of gut microflora, enterocolitis and Salmonellosis in this horse.

Three horses in Group 3 lost weight, but the group gained an average of two pounds during the study. Of the seven horses alive at the end of the study, four were normal, and three were observed for an additional 15 days. These three horses had low serum albumin (1/3), low serum total protein (2/3) or leukocytosis (3/3) at the end of the study. Two of these three horses also had lost weight over the course of the study. All three horses were rechecked eight and 15 days later and had returned to normal

at the 15 day recheck without therapeutic intervention.

(b) Clinical Pathology:

Statistical Analysis Methods: Variables measured only once following treatment were analyzed using analysis of covariance (ANCOVA). Variables measured multiple times following treatment were analyzed using repeated measures ANCOVA. The covariate in both cases was the baseline value of the variable, if measured only once pre-treatment, or the average of two baseline values closest to the initiation of treatment.

Treatment and treatment by time interactions (in the repeated measures analysis) were tested at an alpha level of 0.10. If the time by treatment interaction was significant, treatment groups were compared to control at each measurement time. Otherwise, if the treatment group effect was significant, treatment groups were compared to control, averaged over time. If gender by treatment interaction was significant at the 0.05 level, the analysis was performed separately for each sex and followed the same logic for testing treatment effects as the above.

Combined Sexes Analyses: There were statistically significant effects of the 2X dose that exhibited during the study in the following variables: absolute segmented neutrophils and white blood cells were elevated on days 15 and 35; albumin was decreased on days 22, 29 and 35; eosinophils were decreased on days 22 and 35 (1X group was also decreased on days 4 and 15); and globulin was decreased on days 8, 15, 22, 29 and 35. Differential white blood cell percentages revealed a statistically significant increase in neutrophils and monocytes and a decrease in lymphocytes when averaged over all observation times. The changes in these variables were consistent with the clinical findings.

Separate Sexes Analyses: There were effects of the 2X dose near the end of the study in AST, BUN, prothrombin time and total protein. In females, AST was reduced on days 22 and 35. In males, BUN was reduced on days 4, 15, 25 and 35. In males, prothrombin time was reduced on days 4 and 35. Total protein was reduced on days 29 and 35 in females, and on days 15 and 29 in males. ALT, calcium, and creatine kinase at the 2X dose were significantly lower than control, averaged over all times, in males only. There was no clinical significance of these changes, with exception of the lowered total protein.

Urinalysis values were all within the normal reference range, but the average urine pH was significantly lower in the 2X dose group than in the

other groups. Water consumption in the 2X group horses was elevated pre-study and remained so throughout the study period.

(c) Post-mortem Pathology: Necropsy was not performed.

(5) Conclusions: This study demonstrated that administration of NAVIGATOR Antiprotozoal Oral Paste, when administered according to label directions (11.36 mg/lb for Days 1-5 followed by 22.72 mg/lb for Days 6-28, is safe for use in healthy horses. Conversely, 22.72 mg/lb for Days 1-5 followed by 45.45 mg/lb for Days 6-28, can result in irreversible, fatal enterocolitis despite supportive therapy.

d. **Field Safety Evaluation:**

(1) Field Study I:

In this field study, a total of 81 horses received at least one dose of nitazoxanide. Twenty-two horses (27%) experienced adverse reactions as noted in the table on page 17:

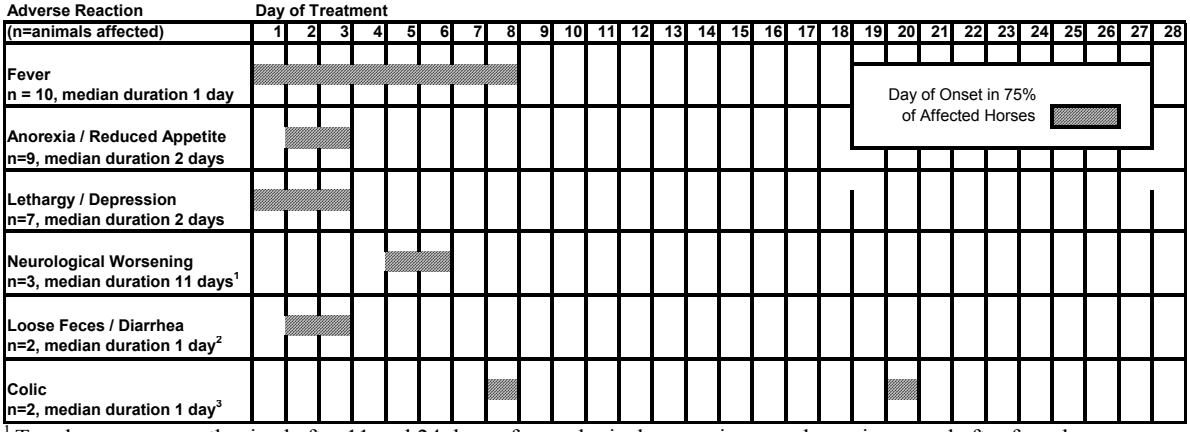
Table 9. Adverse Reactions in Field Study I

Body System	Adverse Reactions	% Incidence in First Field Study (n[1]/81)
Total		27% (22/81)
Alimentary and Urinary	Anorexia	2 (2/81)
	Reduced appetite	9 (7/81)
	Loose feces	0 (0/81)
	Discolored[2] urine or discolored[3], malodorous feces	1 (1/81)
	Colic	2 (2/81)
	Diarrhea	2 (2/81)
	Hematuria, stranguria	1 (1/81)
Circulatory	Shock	0 (0/81)
	Elevated Heart Rate & Respiration Rate	1 (1/81)
Hemolymphatic	Fever	12 (10/81)
	Edematous limbs	7 (6/81)
	Lymphadenopathy	0 (0/81)
	Leukopenia	0 (0/81)
	Facial Edema	0 (0/81)
	Mastitis	0 (0/81)
Musculoskeletal	Sore/warm feet/increased digital pulses	1 (1/81)
	Stiffness	2 (2/81)
	Pastern/joint pain	0 (0/81)
Neurological	Lethargy/depression	9 (7/81)
	Worsening of neurological signs	4 (3/81)
	Behavioral changes	0 (0/81)
Respiratory	Nasal discharge	0 (0/81)

[1]Number of horses
[2]Urine color can change to bright orange or dark yellow due to excretion of nitazoxanide in the urine
[3]Excretion of nitazoxanide in the bile can change feces color from green to brown

Fever, anorexia/reduced appetite and lethargy/depression were the most commonly observed adverse reactions in this study. The following table describes the onset and duration of these adverse reactions.

Table 10. Onset & Duration of Most Common Adverse Reactions in Field Study I



[1] Two horses were euthanized after 11 and 24 days of neurological worsening; one horse improved after four days
[2] Bars represent both affected horses; one horse had diarrhea on Day 2 and one horse had diarrhea on Day 3
[3] Bars represent both affected horses; one horse was colicky on Day 8 and one was colicky for 1 hour on Day 20

Aside from the adverse reactions that occurred in the horses that died or were euthanized, most were reported as isolated events. In some cases, however, certain adverse reactions occurred together. During this study, fever, lethargy/depression and anorexia/reduced appetite were reported to occur together in 3 cases. Fever and anorexia/reduced appetite were also observed concurrently with worsening of neurological signs (one case) and lethargy/depression and diarrhea (one case). In two cases anorexia/decreased appetite was accompanied by fever and worsening of neurological signs, respectively.

Of the 22 horses in the Field Study I that experienced adverse reactions, six resolved without any therapeutic intervention. The clinical signs in the remaining 16 horses were treated with anti-inflammatory drugs such as dexamethasone, flunixin meglumine, phenylbutazone and DMSO. In some cases, intravenous fluids were also administered.

Four horses were euthanized during this study because of worsening neurological conditions. Three of these horses had necropsy findings consistent with chronic EPM. Two of the four also experienced adverse drug reactions.

(2) Field Study II:

In this field study, a total of 416 horses received at least one dose of nitazoxanide. One hundred twenty-nine horses (31%) demonstrated an adverse reaction as noted in the following table.

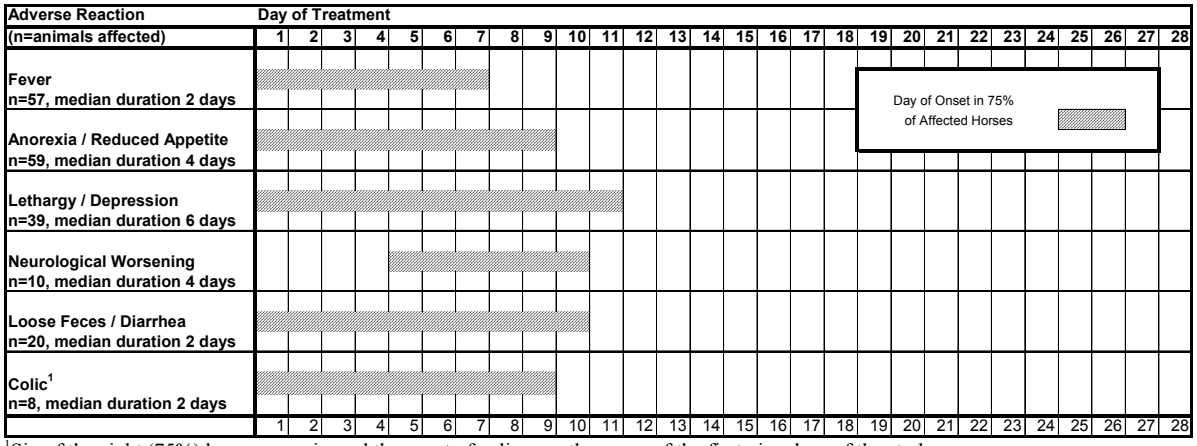
Table 11. Adverse Reactions in the Field Study II

Body System	Adverse Reactions	% Incidence in Field Study II (n[1]/416)
Total		31% (129/416)
Alimentary and Urinary	Anorexia	14 (59/416)[2]
	Reduced appetite	
	Loose feces	3 (14/416)
	Discolored[3] urine or discolored[4], malodorous feces	3 (12/416)
	Colic	2 (8/416)
	Diarrhea	1 (6/416)
	Hematuria, stranguria	0 (0/416)
Circulatory	Shock	<1 (1/416)
	Elevated Heart Rate & Respiration Rate	0 (0/416)
Hemolymphatic	Fever	14 (57/416)
	Edematous limbs	5 (19/416)
	Lymphadenopathy	<1 (2/416)
	Leukopenia	<1 (2/416)
	Facial Edema	<1 (2/416)
	Mastitis	<1 (1/416)
Musculoskeletal	Sore/warm feet/increased digital pulses	2 (10/416)
	Stiffness	<1 (2/416)
	Pastern/joint pain	<1 (1/416)
Neurological	Lethargy/depression	10 (40/416)
	Worsening of neurological signs	2 (9/416)
	Behavioral changes	<1 (2/416)
Respiratory	Nasal discharge	<1 (1/416)

[1] Number of horses
[2] Horses with anorexia and reduced appetite were combined in this study
[3] Urine color can change to bright orange or dark yellow due to excretion of nitazoxanide in the urine
[4] Excretion of nitazoxanide in the bile can change feces color from green to brown

Fever, anorexia/reduced appetite and lethargy/depression were the most commonly observed adverse reactions in this study. The following table describes the onset and duration of these adverse reactions.

Table 12. Onset & Duration of Most Common Adverse Reactions in Field Study II



[1]Six of the eight (75%) horses experienced the onset of colic over the range of the first nine days of the study.

During this field study, anorexia/reduced appetite and lethargy/depression were concurrently reported in four cases. In three of these four cases the clinical signs were also accompanied by loose feces/diarrhea. One febrile horse demonstrated anorexia/reduced appetite along with loose feces/diarrhea and another febrile horse had anorexia/depressed appetite with lethargy/depression and lymphadenopathy. Other adverse reactions were reported as isolated events.

Clinical signs resolved without any therapeutic intervention in 44 of the 129 horses that showed adverse reactions. The remaining 85 horses were managed with anti-inflammatory agents or combination therapy comprised of an anti-inflammatory agent and another class of drug. For example, four of 40 horses demonstrating lethargy/depression were treated with flunixin meglumine, phenylbutazone, dexamethasone, DMSO, ceftiofur, and folic acid. Fever was managed in 19 of 57 horses with flunixin meglumine, phenylbutazone, dexamethasone, and gentamicin. Anorexic horses received flunixin meglumine, dexamethasone, cimetidine, and mineral oil in six of 59 cases. Eight of 21 horses demonstrating edema were treated with flunixin meglumine, phenylbutazone, furosemide, procaine penicillin, trimethoprim sulfa, and bran mash. Six of ten horses with increased digital pulses and sore/warm feet received flunixin meglumine, phenylbutazone, and topical nitroglycerin. Colic was treated with flunixin meglumine, mineral oil, bismuth subsalicylate, and IV fluids in six of the eight cases. Four of nine horses demonstrating neurological worsening received flunixin meglumine, dexamethasone, DMSO, detomidine, and Vitamin E. Various treatment regimens (dosage and combination) were utilized but most were administered for brief periods of time due to rapid resolution of clinical signs. No adjunctive therapy was administered to horses with loose feces or diarrhea.

In addition to the previously mentioned treatments, administration of nitazoxanide was interrupted in 24 febrile horses. The median duration that a horse did not receive nitazoxanide was two days.

Twenty-eight horses died or were euthanized during Field Study II. Five of these cases were possibly associated with the use of nitazoxanide and are summarized below.

One horse became febrile (103°F) on Day 8 of the study and nitazoxanide was stopped. The fever worsened (106°F) and projectile diarrhea developed. The horse was euthanized on Day 11 of the study. Necropsy revealed acute bacterial typhlocolitis. Another horse exhibited lethargy and anorexia on Day 2 of the study, but continued to receive nitazoxanide. On Day 7 of the study, the horse developed diarrhea and on Day 8 developed a fever of 104°F. Despite stopping nitazoxanide and transfer to a referral hospital, the horse died on Day 16. Necropsy revealed fibronecrotic enterocolitis and pneumonia. A six-month old colt was given nitazoxanide for two days after which he developed a fever (101.4°F) and loose feces. The fever worsened and diarrhea developed. The colt died on Day 5 of the study. Necropsy revealed a perforated gastric ulcer and peritonitis. Another horse developed a fever (103.2°F) on Day 2 of the study, and nitazoxanide was continued despite the fever. The fever rose to 106°F, and the horse died on Day 4 of the study. Necropsy revealed granulomatous pneumonia, esophageal erosions and gastric ulcerations. A stallion developed laminitis on Day 4 of the study, and nitazoxanide was immediately discontinued. The condition persisted despite medical intervention and corrective shoeing, and the horse was euthanized two months later due to bilateral distal phalanx rotation.

Seven horses were euthanized due to insufficient recovery for work or protracted neurological disease, but necropsies were not performed. Three horses with worsening neurological conditions were euthanized and had confirmatory findings of chronic EPM on necropsy examination. One horse that was euthanized because of severe behavioral problems was diagnosed post mortem with chronic necrotizing multifocal myelitis of undetermined origin. The remaining 12 horses were euthanized (11) or died (1) as a result of other medical conditions.

e. Conclusions of Safety Studies:

The safety studies provide evidence that toxicity and death can occur at elevated doses of 45.45 mg/lb (2X the regular dose) and higher. Because the product has a narrow margin of safety, accurate dosage calculations and adherence to instructions provided in the product labeling (package insert, client information sheet) are critical for safe use of NAVIGATOR Antiprotozoal Oral Paste.

In the field studies, three clinical signs emerged as predominant adverse reactions. Fever was observed in 13% of the treated horses. Anorexia or reduced appetite was noted in 14% of the horses. Lethargy or depression was the third common finding in the field studies and was noted in 10% of the clinical cases.

Other clinical findings included loose feces, malodorous feces, colic, diarrhea, edema, sore or warm feet, increased digital pulses, joint stiffness, joint pain, or worsening of neurological signs.

Four horses were euthanized during Field Study I due to worsening neurological signs. Twenty-eight horses died or were euthanized during Field Study II. Five of the cases were possibly associated with the use of nitazoxanide. These cases developed intractable clinical signs and were euthanized or died. The final diagnoses at necropsy included: enterocolitis, gastric ulcers, and laminitis.

4. HUMAN SAFETY:

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "For use in animals only. Not for use in horses intended for human consumption. Not for human use. Keep out of reach of children."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste, when administered under labeled conditions is safe and effective for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona.*

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is critical for the diagnosis of equine protozoal myeloencephalitis in horses. The safe use of this product must also be monitored by the veterinarian.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

NAVIGATOR is protected under the following U.S. patent numbers:

US Patent Number	Date of expiration
5, 578, 621	September 8, 2014
5, 935, 591	January 15, 2018
5, 968, 961	May 7, 2017
6, 117, 894	May 7, 2017

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

a. Package Insert
b. Client Information Sheet
c. Syringe Label
d. Foil Pouch
e. Dispensing Box
f. Lid Sticker
g. Weight Tape