

## Package Insert

# Navigator<sup>®</sup>

(32% nitazoxanide)

### Antiprotozoal Oral Paste

**For the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses. For oral use only.**

#### CAUTION

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

#### DESCRIPTION

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste is supplied in ready-to-use syringes containing 85 grams of paste. Each gram of paste contains 320 mg of nitazoxanide (32% w/w). NAVIGATOR (32% nitazoxanide) is an orally administered paste.

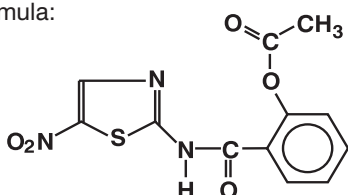
Each syringe of NAVIGATOR Paste contains enough paste to treat one (1) 1,200-pound horse for two (2) days at the starting dose of 11.36 mg/lb or one (1) day at the regular dose of 22.72 mg/lb body weight. The plunger is fitted with a dosage ring designed to deliver a dosage of 22.72 mg/lb and is marked for a horse weighing up to 1,200 pounds. The NAVIGATOR dispensing box contains 26 syringes; which provides 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).

Chemical name: 2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide

Empirical formula: C<sub>12</sub> H<sub>9</sub> N<sub>3</sub> O<sub>5</sub> S

Molecular weight: 307.3

Structural formula:



#### INDICATIONS

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

#### DOSAGE & ADMINISTRATION

Always provide the Client Information Sheet to the animal owner or person treating the horse with each prescription. NAVIGATOR 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

**PLEASE NOTE:** A total of 26 syringes are included in the NAVIGATOR 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 greater than 1,200 pounds.

#### DIRECTIONS FOR USE

- Step 1 Obtain an accurate body weight periodically (once a week) to ensure the correct dose is administered. Use a scale or the weight tape provided in the NAVIGATOR dispensing box.
- Step 2 Open the foil pouch and remove the NAVIGATOR syringe. Set the dosage ring for the appropriate dose according to the following schedule.
- Day 1**—Use the syringe in the space marked #1 and set the dosage ring to **one-half (1/2)** the horse's weight in pounds.
- Day 2**—Use the partially used syringe from Day 1 and set the dosage ring to the **full weight** of the horse in pounds (this will deliver the same amount as administered on Day 1).
- Day 3**—Use the syringe in the space marked #2 and set the dosage ring to **one-half (1/2)** the horse's weight in pounds.
- Day 4**—Use the partially used syringe from Day 3 and set the dosage ring to the **full weight** of the horse in pounds (this will deliver the same amount as administered on Day 3).
- Day 5**—Use the syringe in the space marked #3 and set the dosage ring to **one-half (1/2)** the horse's weight in pounds. Syringe #3 will be only partially used. Save this syringe until dosing is complete and then discard it along with the other syringes.
- Days 6-28**—Use the remaining syringes and set the dosage ring to the **full weight** of the horse in pounds.

To set the dosage ring on the syringe plunger, rotate (dial) the top of the ring to the appropriate dosing mark.



- Step 3 Ensure the horse's mouth contains no feed. Remove the cover from the tip of the syringe and insert the tip into the horse's mouth at the interdental space. Depress the plunger until it is stopped by the dosage ring. The dose should be deposited on the back of the tongue or deep into the cheek pouch.
- Step 4 To aid swallowing of paste, immediately raise the horse's head for a few seconds after dosing.
- Step 5 Clean the tip of the syringe with a clean disposable towel and replace the cover on the tip of the syringe. Return the syringe to the original space in the NAVIGATOR dispensing box.
- Step 6 Repeat until the horse has been treated for 28 days. Weigh the horse weekly and set the dose based upon the current body weight to ensure accurate dosing.
- Step 7 At the end of the treatment period, all empty and partially empty syringes should be discarded. Do not reuse dosing syringes.

## CONTRAINDICATIONS

This product is contraindicated for use in horses less than one year of age and in horses that are sick or debilitated for reasons other than EPM.

## WARNINGS

**Warnings:** Administration of nitazoxanide can disrupt the normal microbial flora of the gastrointestinal tract leading to enterocolitis. Deaths due to enterocolitis have been observed while administering the recommended dose in field studies.

Obtain an accurate body weight and calculate the dose weekly during treatment. Overdosing of nitazoxanide must be avoided. Read the Dosage & Administration and Precautions sections of the package insert before dosing the horse. It is important to monitor the horse for adverse clinical signs during treatment. Read the Adverse Reactions section of the package insert for more information on adverse reactions.

## HUMAN WARNINGS

For use in animals only. Not for use in horses intended for human consumption. Not for human use. Keep out of reach of children.

## PRECAUTIONS

Administration of nitazoxanide to horses can disrupt the normal bacterial flora of the gut resulting in an enteropathy. **If a horse develops any of the following: a high fever (>103°F), scant or loose feces, diarrhea, colic or signs of laminitis, nitazoxanide treatments should be stopped immediately and appropriate veterinary care should be initiated.**

Horses on nitazoxanide treatment should be **monitored for adverse reactions at least once daily for the duration of treatment.** The most common adverse reactions observed were fever, reduced appetite/anorexia and lethargy/depression. Other adverse reactions included decreased gut sounds, scant feces, loose feces/diarrhea, malodorous and/or discolored feces, colic, laminitis, increased water consumption, discolored urine, head and/or limb edema, and weight loss.

If the horse owner or caretaker is not capable of monitoring the horse for the above adverse reactions, provisions should be made to assure adequate monitoring. **Failure to monitor the horse during treatment with NAVIGATOR can result in serious adverse reactions and death.** For a more complete discussion of adverse reactions and deaths see the Adverse Reactions section of this package insert.

If any of the adverse reactions listed above are observed, the **veterinarian should examine the horse immediately.** Examination should consist of a complete physical examination in conjunction with a complete blood count and determination of serum albumin, total serum protein and determination of body weight.

**Treatment of adverse reactions** may include administration of anti-inflammatory drugs (phenylbutazone, flunixin meglumine, DMSO, dexamethasone), probiotic agents, antibiotics and mineral oil. Depending on the severity of the adverse reactions and the overall condition of the horse, therapy with nitazoxanide may need to be discontinued until the clinical signs resolve.

**Stallions may be more prone to develop laminitis while on nitazoxanide** as compared to mares or geldings. Nitazoxanide should be used with caution in stallions and in horses that are predisposed to laminitis.

A horse that is receiving nitazoxanide should not be subjected to stressful situations (e.g. abrupt changes in diet, exercise, stabling arrangements, abnormally long trailer rides, etc.).

The term “**treatment crisis**” has been applied to a cluster of signs consisting of worsening of neurological deficits, fever, lethargy and depressed appetite. This is more common during the first two weeks of treatment. The signs are believed to result from central nervous system inflammation in response to the dead and/or dying protozoa. Depending on the severity of the crisis, anti-inflammatory therapy may be indicated. Dosing may be continued during the “treatment crisis,” providing the horse is closely monitored for appearance of other adverse reactions (i.e. anorexia, diarrhea, colic, laminitis).

The **reproductive safety** of nitazoxanide has not been determined in breeding stallions or in breeding mares or lactating mares.

The pharmacokinetics of nitazoxanide in horses with **compromised renal or hepatic function** has not been studied. Therefore, nitazoxanide must be administered with caution to horses with hepatic and biliary disease, to horses with renal disease, and to horses with combined renal and hepatic disease.

The active metabolite of nitazoxanide is highly protein-bound to plasma proteins; therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur.

The safety of nitazoxanide with concomitant therapies in horses has not been evaluated in laboratory studies.

## ADVERSE REACTIONS

Two field studies were conducted in client-owned horses diagnosed with EPM. Nitazoxanide was administered at the recommended dose. The following adverse reactions were reported.

In **Field Study I**, a total of 81 horses received at least one dose of nitazoxanide. Twenty-two horses (27%) experienced adverse reactions as noted in the tables below.

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 1. Onset and Duration of Most Common Adverse Reactions in Field Study I**

Adverse Reaction	Day of Treatment																																					
(n=animals affected)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28										
Fever n=10 median duration 1 day	█																																					
Anorexia/Reduced Appetite n=9 median duration 2 days	█																																					
Lethargy/Depression n=7 median duration 2 days	█																																					
Neurological Worsening n=3 median duration 11 days*						█																																
Loose Feces/Diarrhea n=2 median duration 1 day**	█																																					
Colic n=2 median duration 1 day***								█																				█										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28										

\*Two horses were euthanized after 11 and 24 days of neurological worsening; one horse improved after four days

\*\*Bars represent both affected horses; one horse had diarrhea on Day 2 and one horse had diarrhea on Day 3

\*\*\*Bars represent both affected horses; one horse was colicky on Day 8 and one was colicky for one hour on Day 20

Day of Onset in 75% of Affected Horses █

Aside from the adverse reactions that occurred in the horses that died or were euthanized, most of the adverse reactions 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 three 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 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.

In **Field Study II**, 416 horses received at least one dose of nitazoxanide. One hundred twenty-nine horses (31%) demonstrated adverse reactions as noted in the following tables.

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 2. Onset and Duration of Most Common Adverse Reactions in Field Study II**

Adverse Reaction (n=animals affected)	Day of Treatment																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	
<b>Fever</b> n=57 median duration 2 days	■	■																											
<b>Anorexia/Reduced Appetite</b> n=59 median duration 4 days	■	■	■	■																									
<b>Lethargy/Depression</b> n=39 median duration 6 days	■	■	■	■	■	■	■																						
<b>Neurological Worsening</b> n=10 median duration 4 days				■	■	■	■																						
<b>Loose Feces/Diarrhea</b> n=20 median duration 2 days	■	■																											
<b>Colic</b> n=8 median duration 2 days	■	■																											

Day of Onset in 75% of Affected Horses

During this study, anorexia/reduced appetite and lethargy/depression were concurrently reported in four cases. In three of the 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 10 horses with increased digital pulses and sore/warm feet received flunixin meglumine, phenylbutazone and topical nitroglycerine. 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.

**Table 3. Incidence of Adverse Reactions Recorded in Field Studies I & II**

Body System	Adverse Reactions	% Incidence in Field Study I (n/81)*	% Incidence in Field Study II (n/416)
		<b>Total</b>	27% (22/81)
<b>Alimentary and Urinary</b>	Anorexia	2 (2/81)	14 (59/416)**
	Reduced appetite	9 (7/81)	**
	Loose feces	0 (0/81)	3 (14/416)
	Discolored urine <sup>†</sup> or discolored <sup>††</sup> malodorous urine/feces	1 (1/81)	3 (12/416)
	Colic	2 (2/81)	2 (8/416)
	Diarrhea	2 (2/81)	1 (6/416)
	Hematuria, stranguria	1 (1/81)	0 (0/416)
<b>Circulatory</b>	Shock	0 (0/81)	<1 (1/416)
	Elevated heart rate and respiratory rate	1 (1/81)	0 (0/416)
<b>Hemolymphatic</b>	Fever	12 (10/81)	14 (57/416)
	Edematous limbs	7 (6/81)	5 (19/416)
	Lymphadenopathy	0 (0/81)	<1 (2/416)
	Leukopenia	0 (0/81)	<1 (2/416)
	Facial edema	0 (0/81)	<1 (2/416)
	Mastitis	0 (0/81)	<1 (1/416)
<b>Musculoskeletal</b>	Sore/Warm feet/Increased digital pulses	1 (1/81)	2 (10/416)
	Stiffness	2 (2/81)	<1 (2/416)
	Pastern/Joint pain	0 (0/81)	<1 (1/416)
<b>Neurological</b>	Lethargy/Depression	9 (7/81)	10 (40/416)
	Worsening of neurological signs	4 (3/81)	2 (9/416)
	Behavioral changes	0 (0/81)	<1 (2/416)
<b>Respiratory</b>	Nasal discharge	0 (0/81)	<1 (1/416)

\*n = # horses

\*\* Horses with anorexia and reduced appetite were combined in this study

<sup>†</sup>Urine color can change from bright orange to dark yellow due to excretion of nitazoxanide in the urine

<sup>††</sup>Excretion of nitazoxanide in the bile can change feces color from green to brown

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 as follows: 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 had a fever of 104°F.

Despite stopping treatment 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 the result of other medical conditions.

**To report suspected adverse reactions or for a copy of the Material Safety Data Sheet (MSDS), call 1-800-374-8006.**

#### INFORMATION FOR CLIENT

The Client Information Sheet provides important information about EPM, the proper administration of NAVIGATOR Paste and adverse reactions that may occur. The prescribing veterinarian should discuss the Client Information Sheet with the person treating the horse when NAVIGATOR Paste is dispensed. The Client Information Sheet is fixed to the inside of the upper flap of the dispensing box and also is included as a separate sheet within the dispensing box.

#### CLINICAL PHARMACOLOGY

**Proposed mode of action:** Using *in-vitro* models, it is probable that nitazoxanide is selectively toxic for organisms capable of intracellular reduction of the nitazoxanide nitro group to a toxic free radical. This activity interferes with cellular respiration of the target organism.

Based upon cell culture data, dosages of nitazoxanide 1.0 ppm or greater prevented measurable monolayer destruction in a lesion-based microassay against *S. neurona* merozoites. In this assay, the concentration of nitazoxanide that inhibited the merozoites by 50% (inhibitory concentration 50; IC<sub>50</sub>) was 0.52 ppm.

**Pharmacokinetics:** Eight (4 males, 4 females) mixed-breed, healthy horses received either a single dose or multiple doses of NAVIGATOR Paste for seven consecutive days. Nitazoxanide is rapidly metabolized to the active metabolite, acetylnitazoxanide. Plasma drug levels of deacetylnitazoxanide were nondetectable by 24 hours post-dosing. 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 4. Pharmacokinetic Parameters**

Pharmacokinetic Parameters Determined by Single and Multiple Doses (7) of NAVIGATOR Paste in Healthy Horses (mean ± SD, N=8)			
Dose (22.72 mg/lb)	C <sub>max</sub> (ppm)	T <sub>max</sub> (hrs)	AUC <sub>0-LOQ</sub> (ppm/hrs)
Single	0.51 ± 0.30	2.13 ± 1.13	1.913 ± 0.53
Multiple	0.97 ± 0.49	3.25 ± 3.57	4.770 ± 2.78

C<sub>max</sub>—Maximum concentration of deacetylnitazoxanide achieved

T<sub>max</sub>—Time maximum concentration was achieved

AUC<sub>0-LOQ</sub>—Area under the curve from time 0 through the last sample with deacetylnitazoxanide concentration above the LOQ.

Based on the C<sub>max</sub> and AUC values of the single and multiple doses, some accumulation does occur. When comparing the individual pharmacokinetic data (C<sub>max</sub>, T<sub>max</sub>, 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.

The C<sub>max</sub> for deacetylnitazoxanide after multiple doses of 22.72 mg/lb was 0.97 ppm (1.9X the IC<sub>50</sub> 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.

#### EFFECTIVENESS

The purpose of antiprotozoal therapy in the management of spinal cord injury associated with protozoal infestation is to kill the causative organism and arrest the progression of the disease. Horses were not expected to return to normal neurological status following treatment. It may take 12 months or more of extensive rehabilitation to restore maximum fitness and strength. The amount of rehabilitation needed will vary according to the neuroanatomical site and severity of damage associated with the disease. The risk of permanent damage to the central nervous system increases the longer the infection continues. The damage may be temporary or permanent, which can affect the ultimate prognosis.

#### Field Study I:

Ninety-six horses were enrolled in the study. Forty-nine horses were included in the final analysis of effectiveness. Horses were of various breeds, ages and sexes from different geographical locations within the United States.

NAVIGATOR 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 Paste for treating EPM was evaluated by a standardized neurological examination and Western blot (WB) assay of the cerebral spinal fluid (CSF).

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

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. 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.

Based on improvement in neurological examination scores and/or a negative result using CSF Western blot assay, 28 of 49 horses (57%) were evaluated as successes. Of the 49 horses, seven (14%) had a negative result from a Western blot assay of the CSF by Day 85. Of these seven, four also had an improved neurological examination score. Twenty-two of the 49 horses (45%) were deemed to have an improved neurological examination by independent evaluation of videotapes and/or negative result from a Western blot assay of the CSF on Day 85. The table below is a summary of this effectiveness study.

**Table 5. Results of Field Study I**

	CSF Conversion and/or Neurological Improvement	CSF Conversion on Western Blot
<b>Clinical investigators</b>	28/49 = 57%	7/49 = 14%
<b>Independent evaluators</b>	22/49 = 45%	7/49 = 14%

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

**Field Study II:**

Four hundred nineteen horses were enrolled in the study. Two hundred fifty horses were included in the final analysis of effectiveness. Horses were of various breeds, ages and sexes from different geographical locations within the United States. A protocol was used for this study similar to Field Study I; however, a videotape record of the neurological examination was not required and a CSF analysis for *S. neurona* was not required.

The results of the study are noted in the table below:

**Table 6. Results of Field Study II**

Study Population	Horses not previously treated for EPM with other drugs	Horses previously treated for EPM with other drugs	All horses that completed the study
<b>Successes</b>	113/135=84%	90/115=78%	203/250=81%
<b>Failures</b>	22/135=16%	25/115=22%	47/250=19%

Eighty-one percent (81%) of the cases were evaluated as successes by improvement in neurological examination scores and/or a negative result from the Western blot assay of the CSF by Day 85. Thirty-eight of the 188 (20%) horses receiving follow-up spinal fluid analysis had a negative result from the Western blot assay of the CSF.

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

**ANIMAL SAFETY**

**Tolerance Study:** Eight horses were given one dose of 113.64 mg/lb (10X the starting dose, 5X the regular dose) and observed for 14 days.

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.

**Toxicity Study I:** In this study, eight horses per group were dosed as follows: Group 1, placebo (sham-dosed) for 60 days; Group 2, one (1) whole syringe of nitazoxanide per day for 60 days (average 28.18 mg/lb, 1.2X the regular dose); Group 3, two (2) whole syringes of nitazoxanide per day for 60 days (average 57.27 mg/lb, 2.5X); Group 4, four (4) whole syringes of nitazoxanide per day for 60 days (average 110.91 mg/lb, 4.9X); Group 5, one (1) whole syringe of nitazoxanide per day for Days 1–7 (average 25.91 mg/lb, 1.1X), then two (2) whole syringes of nitazoxanide per day for Days 8–14 (average 52.27 mg/lb, 2.3X), then three (3) whole syringes of nitazoxanide per day for Days 15–75 (average 78.18 mg/lb, 3.4X). All horses were observed for seven days after the last treatment. There were eight (8) horses per group.

In Group 1 (placebo), none of the eight horses experienced any adverse reactions.

In Group 2 (28.18 mg/lb, 1.2X), 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 Day 4 and 8 of the study. Two of the Group 2 horses voided loose stools periodically between Day 6 and 36 of the study. All eight horses in Group 2 recovered without therapeutic intervention.

In Group 3 (57.27 mg/lb, 2.5X), six of eight 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 dosing was discontinued (lactated Ringer's solution for 6–10 days, kaolin pectin for 0–7 days, potentiated sulfonamide for 0–3 days and flunixin meglumine for 0–2 days), and one died. The remaining horses survived without therapeutic intervention.

In Group 4 (110.91 mg/lb, 4.9X), dosing was discontinued on study Day 4 because animals 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 Ringer's, carafate, kaolin pectin); they also received a 12-day course of potentiated sulfonamide.

In Group 5, the 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). 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, 23 and 31. They developed significant weight loss, anorexia, lethargy and decreased gut sounds. These three horses recovered with supportive therapy (lactated Ringer's solution, kaolin pectin and potentiated sulfonamide). Twenty-three days later, one horse developed gastroenteritis and salmonellosis, and died.

Hypoproteinemia was observed in horses in the higher dose groups and was likely a result of a protein-losing enteropathy. Stress leukograms were also observed in the more severely affected horses. Gross and histopathological examination of animals that died in the study clearly indicates the colon as the target tissue. In animals with severe colonic lesions, 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.

**Toxicity Study II:** In this study, horses were dosed as follows: Group 1 (sham-dosed for 28 days), Group 2 (11.36 mg/lb Days 1–5, then 22.72 mg/lb Days 6–28; 1X starting and regular dose), Group 3 (22.72 mg/lb Days 1–5 then 45.45 mg/lb Days 6–28; 2X starting and regular dose). All horses were observed for seven days after the last treatment. There were eight horses in each treatment group.

All horses in all groups completed the dosing portion of the study. In Group 1 (sham-dosed), 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 feces (normal color of freshly voided feces was considered to be green). 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.

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.

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.

There was a statistically significant lymphopenia observed in Group 3 horses at mid-study, and neutrophilia at the end of the study, although all mean values remained within normal reference range. Statistical evaluation of the clinical chemistry values showed decreased serum albumin, globulin and total protein at the end of the study, although the average albumin levels remained within the normal reference range. Three horses in Group 3 had serum total protein and serum albumin values below the normal reference range near the end of the study period. Urinalysis values were all within the normal reference range, but the average urine pH was significantly lower in Group 3. Water consumption in Group 3

horses was elevated pre-study and remained so throughout the study period. Three horses in Group 3 lost weight, but the group gained an average of two pounds during the study.

One horse in Group 3 developed enterocolitis at 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 after the end of the treatment period. Diagnostic testing, complete necropsy and histopathology revealed findings consistent with alteration of gut microflora, enterocolitis and salmonellosis in this horse.

With the exception of two horses in Group 3 that received supportive therapy (one horse treated with hydrotherapy for edema, another treated with oral electrolytes for five days) and the horse described above that developed enterocolitis, all horses finished the study without supportive therapy.

At the end of the study, the three horses in Group 3 that had detectable abnormalities consisting of low serum albumin (1/3), low serum total protein (2/3) or leukocytosis (3/3) were monitored for an additional 15 days. All three of these horses returned to normal at the end of the 15 days without therapeutic intervention.

## STORAGE INFORMATION

Store below 30°C (86°F). Do not freeze.

## HOW SUPPLIED

NAVIGATOR (32% nitazoxanide) Antiprotozoal Oral Paste for horses contains 32% w/w nitazoxanide and is available in an oral-dose syringe. Each syringe 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 a dosage rate of 22.72 mg/lb, and is marked for a horse weighing up to 1,200 pounds. The NAVIGATOR dispensing box contains 26 syringes, which provides sufficient paste to treat one 1,200-pound horse for 28 days (five days at 11.36 mg/lb and 23 days at 22.72 mg/lb).

## REFERENCE

1. Tizard IR. *Veterinary Immunology*. 4<sup>th</sup> ed. Philadelphia, Pa: WB Saunders; 1992:104–105, 210–211, 327–329.

Manufactured for: IDEXX Pharmaceuticals, Inc.  
Greensboro, NC 27410 USA

Manufactured by: PM Resources, Inc.  
Bridgeton, MO 63044 USA

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