Date of Approval: November 5, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-240

REBALANCE
Antiprotozoal Oral Suspension
(sulfadiazine and pyrimethamine)

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

Sponsored by:

Animal Health Pharmaceuticals, LLC

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-240
b.	Sponsor:	Animal Health Pharmaceuticals, LLC 1805 Oak Ridge Circle, suite 101 St. Joseph, MO 64506 Drug Labeler Code: 068718
c.	Established Name:	Sulfadiazine and pyrimethamine
d.	Proprietary Name:	REBALANCE Antiprotozoal Oral Suspension
e.	Dosage Form:	Oral suspension
f.	How Supplied:	REBALANCE Antiprotozoal Oral Suspension is supplied in 946.4 mL (1 qt) bottles.
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	Each mL of REBALANCE Antiprotozoal Oral Suspension contains 250 mg sulfadiazine (as the sodium salt) and 12.5 mg of pyrimethamine.
i.	Route of Administration:	Oral
j.	Species:	Equine
k.	Recommended Dosage:	The recommended dosage is 20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine daily or 4 mL of REBALANCE Antiprotozoal Oral Suspension per 110 lb (50 kg) of body weight per day. The duration of treatment is dependent upon clinical response, but the usual treatment regimen ranges from 90 to 270 days. Administer at least one hour prior to feeding hay or grain.
l.	Pharmacological Category:	Antiprotozoal
m.	Indications:	REBALANCE Antiprotozoal Oral Suspension is indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

2. EFFECTIVENESS:

a. Dosage Characterization:

Sulfadiazine (20 mg/kg) and pyrimethamine (1 mg/kg) once per day for a minimum of 90 days is the empirical regimen of therapy currently recommended in the scientific literature for the treatment of EPM[1]. Sulfadiazine and pyrimethamine are two different antimicrobial agents which inhibit folic acid synthesis at two different sites in the same synthetic pathway. The combination of sulfadiazine and pyrimethamine is synergistic, with the drug combination having an antiprotozoal effect. Because of the greater frequency and severity of bone marrow suppression at the 2X dose level, REBALANCE Antiprotozoal Oral Suspension should be administered at the labeled 1X dose level, sulfadiazine (20 mg/kg) and pyrimethamine (1 mg/kg) once per day for a minimum of 90 days.

b. Substantial Evidence:

(1) Historical Control:

EPM is usually a progressive neurological disease. It has been estimated that up to 55 to 65%[2] of horses respond favorably to treatment. However, it is further estimated that a small percentage (no more than 10%) of treated horses recover completely. One of the most important points to consider is that EPM produces a 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: Clinical Field Effectiveness and Safety of Daily Pyrimethamine and Sulfadiazine Oral Suspension in Horses Affected with EPM

(a) Type of Study:

This study was conducted as a multi-site, randomized field effectiveness evaluation of two dose levels of REBALANCE Antiprotozoal Oral Suspension. The two dose levels (1X) 20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine and (2X) 40 mg/kg sulfadiazine and 2 mg/kg pyrimethamine were administered daily for a minimum of 90 days.

(b) Investigators:

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[1] MacKay RJ, Granstrom DE, Saville WJ, Reed SM. Equine Protozoal Myeloencephalitis: *Veterinary Clinics of North America/Equine Practice*, 2000:16:405-425.

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

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(c) Study Design:

1 Purpose: This study was designed to evaluate the clinical effectiveness and safety of sulfadiazine and pyrimethamine for the treatment of horses with EPM at a dosage of 20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine or 40 mg/kg sulfadiazine and 2 mg/kg pyrimethamine administered in a daily oral dosage for a minimum of 90 days.

2 Test Animals: There were 97 horses enrolled in this study, consisting of 34 females, 13 males and 50 geldings ranging from nine months to 32 years of age. Seventy-two percent of the horses were Thoroughbreds, Standardbreds and Quarter Horses, with the remainder represented by Tennessee Walker Horses, Appaloosas, Arabians and mixed breeds.

3 Enrollment Criteria: Initial selection of the animals into the field effectiveness study was based upon a qualifying physical examination and on a clinical neurological examination. Blood and cerebrospinal fluid (CSF) samples were collected for determination of serum and CSF serological status for EPM (Western Blot Test),

albumin quotient (AQ) and immunoglobulin G (IgG) index. In addition, blood samples were collected for complete blood count (CBC) and serum chemistry profile to assess the overall health of the animals prior to initiating treatment.

Subsequently, a diagnosis of EPM was confirmed by a positive Western Blot Test for *Sarcocystis neurona* on CSF and clinical signs compatible with EPM. Animals were admitted to the study prior to receipt of results of CSF Western Blot Test, but eligibility was revoked upon receipt of a negative CSF Western Blot Test. The severity of the neurological deficit was determined by the overall neurological dysfunction (OND) score.

Neurologic Grading Score for OND:
0 = clinically normal. No detectable dysfunction.
1 = slight deficit. Dysfunction barely perceptible.
2 = moderate deficit. Dysfunction easily detectable.
3 = marked deficit. Dysfunction strikingly conspicuous.
4 = severe deficit. Profound dysfunction.
5 = recumbent.

4 Exclusion Criteria: Animals outside of study specifications, such as pregnant mares, horses with clinical histories incompatible with EPM diagnosis, or CSF Western Blot Test negative serological status, were excluded from the field effectiveness study. Animals whose owners/authorized agents had not signed the informed consent document were also excluded from the study. Animals which had condition(s) other than EPM that might interfere with the clinical determination of severity of the neurological deficit caused by EPM and the response to treatment, were also excluded from the study. Animals which had been treated for EPM condition for more than 30 days immediately prior to admittance to this clinical effectiveness study were also excluded from the study.

5 Treatment Groups and Controls: Ninety-seven (97) horses met the clinical effectiveness study entrance criteria. Each horse admitted to the study had a baseline clinical evaluation consisting of a clinical description and characterization of myoneural abnormalities, a videotape recording of the neurological deficit, a physical examination, a CBC, a serum chemistry analysis, a CSF and a serum Western Blot Test and a determination of CSF indices (AQ and IgG index protein electrophoresis) prior to assignment to a treatment group.

Treatment dosage of sulfadiazine and pyrimethamine (1X and 2X)

was predetermined by a randomized treatment schedule. Forty-eight (48) horses were assigned to the 1X treatment group (20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine); forty-nine horses were assigned to the 2X treatment group (40 mg/kg sulfadiazine and 2 mg/kg pyrimethamine). The scheduled dosage regimen was for daily oral administration for a duration of 90 to 180 days. In 14 horses, the duration of administration exceeded 180 days, with the duration of administration ranging from 195 to 270 days.

6 Dosage Form: The oral suspension formulation used during this study was identical to the product intended for marketing. REBALANCE Antiprotozoal Oral Suspension contains 250 mg/mL sulfadiazine (as the sodium salt) and 12.5 mg/mL pyrimethamine.

7 Route of Administration: REBALANCE Antiprotozoal Oral Suspension was administered by the oral route via syringe.

8 Dose, Frequency and Duration: The horses were dosed with either 1X (20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine) or 2X (40 mg/kg sulfadiazine and 2 mg/kg pyrimethamine) daily for a duration of 90 to 270 days. Horses were dosed at least one hour prior to feeding hay or grain.

9 Treatment Success: The primary effectiveness variables for the determination of response to test article treatment were the CSF Western Blot Test results and the overall assessment of neurological dysfunction (OND score). A horse was considered a success if any of the following criteria applied at the time the horse was evaluated:

- Negative CSF Western Blot Test and clinical neurological improvement (one or more grade improvement in OND score)
- Negative CSF Western Blot Test and no clinical neurological improvement (zero or less improvement in OND score)
- Positive CSF Western Blot Test and marked clinical neurological improvement (two or more grades improvement in OND score)

All neurological examinations were videotaped. In order to corroborate the investigators' OND scores, independent experts were asked to view the videotapes and confirm that the horses that were deemed to be clinical successes by the investigators appeared to improve on videotape. If the independent experts agreed that the horse showed improvement, the horse was considered a corroborated success.

(d) Results:

Forty-eight horses were assigned to the 20 mg sulfadiazine/kg and 1 mg pyrimethamine/kg dose of REBALANCE Antiprotozoal Oral Suspension (1X treatment group). The final database consisted of 26 horses treated at the 1X dose, the other 22 horses in the 1X group failing to complete the study. Day 0 was the day the horse was first administered test article. Evaluations were made every 30 days. All horses were treated with drug at least 90 days.

Table 1. Summary of Effectiveness Outcomes for 26 horses treated at the 1X dose.

Day of Evaluation	30	60	90	120	150	180	>210	Totals
CSF Successes	-	-	2	1	2	-	-	5
OND Successes	1	1	2	3	2	1	1	11
Uncorroborated OND Successes	-	-	-	-	-	1	1	2
Failures	-	-	-	2	1	3	4	10
OND Successes & CSF Successes	1	1	4	4	4	1	1	16
Corroborated OND Successes & CSF Successes	1	1	4	4	4	0	0	14

Based on the clinical investigator's evaluations and the results of the CSF Western Blot Analysis, 16/26 (61.5%) of horses treated at the 1X dose were successes. Based on the corroborated clinical investigator's evaluation and the results of the CSF Western Blot Analysis, 14/26 (53.8%) of horses treated at the 1X dose were successes. The 95% Blyth-Still-Casella confidence interval for the cumulative percent of corroborated successes is (33.4%, 71.8%).

(e) Adverse Reactions:

Adverse reactions pertaining to bone marrow suppression were two or more times more frequent in the 2X treatment group than the 1X treatment group. Adverse reactions were categorized under the following categories: bone marrow, appetite, gastrointestinal, integument, treatment crisis and unusual daily observations.

Although 97 horses were enrolled in the study (48 in the 1X treatment group, 49 in the 2X treatment group), only 75 horses were administered the drug in the two treatment groups for a duration of at least 90 days, thus a total of 75 horses were evaluated for adverse reactions. Adverse reactions were evaluated in 37 horses treated with the 1X dosage, which included 5,910 daily observations, and 38 horses treated with the 2X dosage, which included 6,210 daily observations.

1 Bone Marrow: Bone marrow suppression due to test article administration caused overall anemia (classification of anemia based on RBC, Hgb, PCV/HCT variables) in 12% of the scheduled observations in the 1X group and 21% of the scheduled observations in the 2X group. In the 37 clinical cases that were treated with 1X dose of test article 90 or more days, anemia was noted in 22%, leukopenia in 19%, neutropenia in 5% and thrombocytopenia in 3% of the cases. Similarly, in the 38 clinical cases in the 2X treatment group, anemia was noted in 58%, leukopenia in 55%, neutropenia in 29% and thrombocytopenia in 5% of the cases. The incidence of bone marrow suppression in the 2X treatment group was two or more times that of the 1X treatment group and the degree of suppression was more serious (mild to severe vs. mild to moderate). Because of these blood dyscrasias, test article was interrupted over four times more often in horses treated at the 2X dosage than those treated at 1X, although both groups were off treatment for about the same amount of time (~20% of the treatment period). In some instances of bone marrow suppression, diet was supplemented with folinic acid to aid in recovery of the bone marrow. Interruption of test article administration with or without folinic acid supplementation proved adequate in preventing any detrimental effects to the overall health and well being of the test animals. Blood counts were not low enough for a long enough period of time to allow development of clinical signs.

2 Appetite: Anorexia was reported in 0.24% of the daily observations for this category in the 1X treatment group (two out of 37 horses) and in 0.03% of the daily observations for the 2X treatment group (one out of 38 horses). The one horse in the 2X treatment group exhibiting anorexia had a concurrent fever associated with liver disease/cholestasis and/or enterotoxemia (hepatocellular disease). Decreased appetite (off feed) was reported in 0.10% of the daily observations for the 1X treatment group (one out of 37 horses) and in 0.05% of the daily observations for the 2X treatment group (one out of 38 horses).

3 Gastrointestinal: Loose stools were observed in three out of 37 horses in the 1X treatment group and five out of 38 horses in the 2X treatment group. Twenty-four of the 26 loose stool observations in both treatment groups occurred between Day 0 and Day 30. Fifteen loose stool observations occurred in one horse in the 1X treatment group between Day 0 and Day 30. Diarrhea was observed in one out of 38 cases in the 2X treatment group (one observation on Day 4).

4 Integument: Urticaria was observed in one out of 37 horses in the 1X treatment group and in two out of 38 horses in the 2X treatment group. One of the horses received conservative topical treatment and two horses received no treatment. The urticaria resolved without sequelae.

5 Treatment Crisis (marked worsening of the neurological condition during treatment believed to be due to an inflammatory reaction in the CNS to the dead/dying protozoan organisms): One horse in the 1X treatment group became progressively more neurologic and recumbent after 99 days of treatment. The worsening of the neurologic signs was assumed to be due to inflammation in the central nervous system associated with dead or dying protozoa. The horse was euthanized on test day 114.

6 Unusual Daily Observations: The following daily observations were also noted. Lethargy/mild depression was observed in five horses; seizure occurred in one horse; mild colic was observed once in three individual horses; elevated liver enzymes associated with acute onset of hepatocellular disease was observed in one horse; increased urination/defecation was observed in one horse; fever was observed in four cases (two with upper respiratory infection, one with hepatocellular disease and one of unknown etiology); neutrophilia associated with inflammation, infection, and/or stress was observed in five horses; leukocytosis associated with upper respiratory infection or hepatocellular disease was observed in two horses; and itchiness/delayed shedding was observed in one horse.

7 Serum Chemistry: There was no test article affect on any of the clinical chemistry variables.

(f) Conclusions:

Based on the clinical investigator's evaluations and the results of the CSF Western Blot Analysis, 16/26 (61.5%) of horses treated at the 1X dose were successes. Based on the corroborated clinical investigator's evaluation and the results of the CSF Western Blot Analysis, 14/26 (53.8%) of horses treated at the 1X dose were successes. The total number of horses that became CSF Western Blot negative was five out of 26 or 19.2%.

REBALANCE Antiprotozoal Oral Suspension is effective for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

3. *TARGET ANIMAL SAFETY:*

(a) Type of Study: Toxicity

(b) Investigator and Trial Location:

Dr. Steven G. Kamerling
Department Of Physiology, Pharmacology and Toxicology
School of Veterinary Medicine
Louisiana State University
Baton Rouge, LA

(c) Study Design

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

2 Purpose: The purpose of the study was to evaluate the safety of REBALANCE Antiprotozoal Oral Suspension in horses.

3 Test Animals: Fourteen healthy Thoroughbred and Quarter Horse test animals (seven males and seven females), ranging in age from three to 16 years.

4 Dosage Form: The test article was an oral suspension.

5 Route of Administration: The test article was administered orally.

6 Dosage, Frequency and Duration of Treatment: Ten horses (five males and five females) were administered REBALANCE Antiprotozoal Oral Suspension at a dosage of 8 mL/50 kg (110 lbs) a day (2X the labeled dose) for 92 days. Treatments were given at least one hour prior to feeding of hay and grain.

7 Controls: Four horses (two males and two females) were not treated.

8 Evaluation of Variables: The health of each animal was evaluated daily. A complete physical examination was conducted and blood was drawn for CBC and serum chemistry analyses three times prior to treatment on test days minus 14 and minus 7 for study eligibility and on Day 0 (immediately prior to start of treatment). The average of the two baseline measurements on test days minus 14 and minus 7 were used as the covariate for each response variable. The physical examinations and blood analyses were repeated at 14-day intervals during treatment and 14 and 29 days following the end of treatment (total of eight physical examination/blood sample observations/analyses per animal during/following treatment).

9 Statistical Methods: CBC and clinical chemistry variables were analyzed using analysis of covariance. Treatment and treatment by time interactions were considered significant if their p-values were less than or equal to 0.10.

(d) Results:

1 Physical Examinations: The observations from biweekly physical examinations were not associated with any clinically significant condition in either group.

2 Complete Blood Count (CBC): CBC variables were analyzed using repeated measures analysis of covariance. Both the treated and control groups experienced a decline in RBC starting on Day 70; however, the treated group was statistically significantly lower ($p \leq 0.10$) than the control group on Days 105 and 120. Hgb also decreased in both groups; however, it was statistically significantly lower ($p \leq 0.10$) in the treated group on Days 28 and 120. PCV and HCT decreased along with the RBC; however, there were no statistically significant differences between treated and control groups. MCV values remained within normal limits for both groups; however, MCV values were slightly elevated in the treated group on Days 70, 84, 105 and 120. Despite the findings of the CBC, there were no clinical signs of anemia observed in either group. Twenty-nine days after cessation of treatment, all values returned to or above baseline levels in both groups. There were no clinically significant changes in white blood cells.

3 Clinical Chemistry: Most serum chemistry variables remained within normal limits throughout the study in both treated and untreated groups. There was considerable variation between groups and from baseline values in both groups, e.g., creatinine, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total protein, globulin and albumin. Elevated ALP values were observed in three of the ten treated horses. These values were slightly above the upper end of the normal range on study days 84 and 105.

4 Daily Observations: Daily animal care observations indicated that the test article was well tolerated for the duration of the treatment period. The most significant observation was the transient appearance of loose stools in both the treated and untreated groups, although the frequency of occurrence was greater in the treated group. Diarrhea was infrequently observed in the treated group and not observed in the untreated group. At no time during the study was the occurrence of loose stools or diarrhea worthy of medical intervention and all cases resolved without sequelae.

5 Appetite: Depressed appetite occurred infrequently in all but one of the treated horses during the study period (affected horses had a depressed appetite for one or two days during the 92-day treatment period). Depressed appetite was not observed in the untreated group. In one of the treated horses, depressed

appetite progressed to anorexia. Daily ration for the anorectic horse was changed from a pelleted ration to a sweet feed ration and appetite was restored.

6 Unusual Observations: One transient case of urticaria in a treated horse was observed on Day 41. This resolved without treatment within 24 hours. Another treated horse became acutely ataxic on Day 88 and died within two hours. Post-mortem examination revealed focal hemorrhage of the brainstem and cerebellum, a lesion consistent with the clinical signs observed prior to death. The precise cause of this cerebrovascular accident was not determined. This horse was also reported to have oral ulcers on Day 45 of the study.

(e) Conclusions:

REBALANCE Antiprotozoal Oral Suspension, administered at 2X the recommended label dose for 92 days resulted in clinical signs of toxicity including: partial to complete anorexia, loose stools and diarrhea, mild to moderate anemia and elevated ALP levels. None of these adverse effects required medical intervention.

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 horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of the 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 REBALANCE Antiprotozoal Oral Suspension, when administered under labeled conditions is safe and effective for the treatment of horses with 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 should also be monitored by the veterinarian.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

REBALANCE Antiprotozoal Oral Suspension is protected under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,747,476	July 17, 2016
6,255,308	July 17, 2016
6,448,252	July 17, 2016

6. ***ATTACHMENTS:***

Facsimile labeling is attached as indicated below:

a. Bottle Label
b. Package Onsert