

Date of Approval: April 28, 2014

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL NEW ANIMAL DRUG APPLICATION**

NADA 141-427

OSPHOS

Clodronate injection

Horse

For the control of clinical signs associated with navicular syndrome in horses.

Sponsored by:

Dechra, Ltd.

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I. GENERAL INFORMATION

A. File Number

NADA 141-427

B. Sponsor

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Drug Labeler Code: 043264

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C. Proprietary Name

OSPHOS

D. Established Name

Clodronate injection

E. Pharmacological Category

Bisphosphonate

F. Dosage Form:

Injection

G. Amount of Active Ingredient

60 mg clodronate disodium per mL

H. How Supplied

20 mL vial containing 15 mL clodronate disodium

I. Dispensing Status

Rx

J. Dosage Regimen

Administer 1.8 mg/kg by intramuscular injection up to a maximum dose of 900 mg per horse. Divide the total volume equally into three separate injection sites.

K. Route of Administration

Intramuscular injection

L. Species/Class

Horse

M. Indication

For the control of clinical signs associated with navicular syndrome in horses.

II. EFFECTIVENESS

A. Dosage Characterization

The dosage characterization is based on two pilot studies: one dose titration study and one dose confirmation study. These two studies established a dose of 1.8 mg/kg (maximum dose 900 mg) as the effective dose of OSPHOS for further evaluation in the clinical field study described in the Substantial Evidence section.

1. Op-03/2006 DT: Dose titration study of a preparation containing clodronate disodium for intramuscular injection in horses suffering from navicular syndrome

A total of 29 adult horses with navicular syndrome received a single intramuscular injection of placebo (isotonic saline), 300 mg, 900 mg, or 1500 mg of OSPHOS. The dose was divided among 5 injection sites and administered intramuscularly. The 900 mg dose of OSPHOS was found to be the lowest effective dose and was selected for the dose confirmation study. There were no reports of local irritation at the injection sites. Colic was reported in two enrolled horses (one placebo-treated horse and one horse treated with 1500 mg OSPHOS).

As a sub-study within the dose titration study, 12 of the 29 horses were randomly chosen for pharmacokinetic evaluation: 3 horses in the 300 mg group, 6 horses in the 900 mg group, and 3 horses in the 1500 mg group. Blood samples were collected at the following time points: prior to administration, and 0.5, 1, 3, 6, 12, 24, and 48 hours post-administration. At the proposed dose of 900 mg, the maximum concentration (C<sub>max</sub>) was 7.46 µg/mL, the area under the plasma concentration (AUC) was 22.85 hr\*µg/mL, the plasma half-life (t<sub>1/2</sub>) was 11.82 hours, and the time to maximum concentration (T<sub>max</sub>) was 0.58 hours. Following a single intramuscular dose, there was a dose proportional increase in the C<sub>max</sub> and AUC with a corresponding increase in dose, indicating that the pharmacokinetics of clodronate disodium were linear within a dose range of 300 to 1500 mg in horses.

2. Op-03/2006 DC: Dose confirmation study of a preparation containing clodronate disodium for intramuscular injection in horses suffering from navicular syndrome

A total of 23 adult horses with navicular syndrome were treated with either an intramuscular injection of 900 mg OSPHOS or placebo (isotonic saline). No adverse reactions were reported in this study. The group of horses treated with 900 mg OSPHOS was improved compared to the placebo treated group. This study was used to justify the dose tested in the field effectiveness study.

#### B. Substantial Evidence

##### 1. Clinical Field Study

- a. Title: An evaluation of the clinical efficacy of OSPHOS for the control of the clinical signs associated with navicular syndrome in horses. Study No.: CLR001

- b. Study Dates: January 19, 2010 to June 22, 2011

- c. Investigators:

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- d. Study Design:

- (1) *Objective:* To evaluate the effectiveness of OSPHOS in controlling the clinical signs associated with navicular syndrome.

- (2) *Study Animals:* One hundred forty-six horses of various breeds enrolled in the study. Horses ranged in age from 4 to 22 years of age and weighed 807 to 1322 pounds. Forty-nine percent of enrolled horses were American Quarter Horses.

(3) Treatment Groups:

Table 1. Treatment Groups

Treatment Group	Dose	Maximum Dose per Horse	Number of Evaluable Animals (Number enrolled)
OSPHOS	1.4 mg/kg	900 mg	86 (111)
Saline	0 mg/kg	0 mg	28 (35)

(4) Drug Administration: Horses were administered 1.4 mg/kg OSPHOS, up to a maximum dose of 900 mg per horse, or an equal volume of saline by intramuscular injection once on Day 0. Doses for all horses were split evenly into three injection sites. Upon completion of the effectiveness portion of the study (Day 56 for horses failing the Day 56 lameness exam or Day 180 for horses successful at the Day 56 exam), owners had the option of administering a supplemental dose of OSPHOS to their horse. Horses receiving a supplemental dose of OSPHOS were monitored for adverse reactions; however, no additional effectiveness data was collected.

The recommended dose of OSPHOS is 1.8 mg/kg with a maximum dose per horse of 900 mg. This study tested a dose of 1.4 mg/kg to evaluate the effectiveness of the lowest dose that a large horse would receive in the field (900 mg/650 kg = 1.4 mg/kg).

(5) Inclusion Criteria:

Horses diagnosed with navicular syndrome, and the absence of other causes of lameness, were eligible for enrollment. Navicular syndrome was diagnosed based on the following criteria:

- Unilateral or bilateral forelimb lameness of  $\geq$  Grade 2 using the American Association of Equine Practitioners (AAEP) Lameness Scale (0 to 5 scale). The primarily lame limb (most lame limb) at the initial visit was assessed at all evaluations for the duration of the study. Investigators had the option of performing a nerve block on the least lame limb to determine the lameness grade of the primarily lame limb at enrollment. If a nerve block was performed on the least lame limb at enrollment, then the block was repeated at all subsequent evaluations.
- Positive response to anesthesia of the distal palmar digital nerves.
- Radiographic evidence of degenerative changes associated with navicular syndrome that are limited to bony changes affecting the navicular bone (e.g., an elevated number of or abnormally shaped lucent zones, subcortical stenosis, enthesiophyte formation) involving the distal sesamoid (navicular) bone.

(6) Exclusion criteria:

- Hind limb lameness or musculoskeletal conditions that could have confounded the lameness exams.
- Horses less than 4 years of age.
- Evidence of neurectomy.
- A change in shoeing/trimming pattern within 2 weeks of enrollment. Shoeing/trimming was required to remain consistent throughout the study.
- Radiographic signs that were indicative of lameness due to primary soft tissue injury, osteoarthritis, fractures, or any condition other than the bony changes related to navicular syndrome.
- Use of concurrent medications to treat navicular syndrome or drugs that could mask lameness pain (e.g., isoxsuprine, tiludronic acid, nitroglycerine, steroids, NSAIDs, etc.). These medications were prohibited throughout the study.

(7) Measurements and Observations:

Horses were treated on Day 0 and effectiveness was assessed on Day 56. Physical examinations and lameness evaluations were performed on all horses at the initial visit (Day -7 to Day -1), Day 28, and Day 56. Clinical pathology assessments were performed on all horses at the initial visit (Day -7 to Day -1) and Day 56. Horses considered a treatment success on Day 56 also received a physical examination and lameness evaluation on Day 180. Radiographs were obtained on all horses at the initial visit. Horses were observed for adverse reactions by the Investigator for the 30 minutes following treatment administration. Owners/Agents observed horses intermittently for the following 2 hours and at least once daily for the next 3 days.

Effectiveness was assessed at Day 56. Horses were considered a treatment success if lameness in the primarily affected limb improved by at least 1 AAEP grade, and there was no worsening of the lameness grade in the contralateral forelimb as compared to the baseline value. Horses that were treatment successes on Day 56 continued on study and were evaluated for maintenance of treatment success on Day 180.

Horses that were treatment failures on Day 56 could receive a supplemental treatment of OSPHOS and were evaluated for safety through Day 180. Horses that were treatment successes at Day 56 could receive a supplemental treatment of OSPHOS after completion of the study at Day 180. These horses were evaluated for safety through Day 240.

(8) Statistical Analysis:

The treatment success rates at Day 56 were analyzed using a generalized linear mixed model, assuming a binomial distribution and employing a logit link. The statistical model included treatment group as a fixed effect and study site and the site-by-treatment interaction as random effects. Degrees of freedom were estimated using the Kenward Rogers method. A "residual" term was included as an additional random effect to account for overdispersion. The treatment effect was tested at a two-sided 5% significance level.

e. Results:

Of the 211 horses screened for enrollment, 146 horses received treatment (111 OSPHOS and 35 saline control). Twenty-nine percent of horses screened for enrollment were not eligible based on radiographic findings. One hundred fourteen horses (86 OSPHOS, 28 saline control) were included in the statistical analysis. Effectiveness was evaluated on Day 56 post-treatment. On Day 56, 68 of the 86 OSPHOS treated horses and 1 out of 28 saline treated horses were treatment successes. Based on the statistical analysis, the estimated least squares mean success rates are 74.7% and 3.3% for the OSPHOS and saline treated groups, respectively. The difference in success rates is significant at P=0.0028.

Table 2. Day 56 Treatment Success Rate

Study Day	OSPHOS	Saline	P value*
56	74.7%	3.3%	0.0028

\* P-value and estimated success rates are based on back-transformed mean estimates from the statistical analysis.

Treatment success based on Day 28 and Day 180 lameness scores were also assessed but not statistically analyzed. At Day 28, 67.4% (60/89) OSPHOS treated horses were considered successes, compared to 20.7% (6/29) in the saline treated group. Day 56 treatment successes were followed to the Day 180 assessment, and Day 56 treatment failures were assumed to remain failures at Day 180. Of the 68 OSPHOS treated horses that were deemed treatment successes on Day 56, 60 were evaluable at Day 180. Of these 60 horses, 51 remained treatment successes at Day 180 based on improvement in lameness grade as compared to Day 0. However, 21 of these 60 evaluable horses demonstrated an increase in lameness grade at Day 180 as compared to their Day 56 evaluation. Including the 18 treatment failures at Day 56, the estimated overall success rate for OSPHOS at Day 180 is 65.4% (51/78).

Table 3. Day 28 and Day 180 Treatment Success Rates

Study Day	OSPHOS	Saline
28	67.4% (60/89)	20.7% (6/29)
180	65.4% (51/78)*	None evaluable

\*The 18 horses that were treatment failures on Day 56 were considered to remain treatment failures at Day 180. No Day 180 lameness evaluation was performed on these horses. Sixty horses (all OSPHOS treated horses) completed the Day 180 lameness evaluation.

f. Adverse Reactions:

All 146 horses (111 OSPHOS, 35 saline control) enrolled in the field study were evaluated for adverse reactions.

Following the Day 0 treatment, 10 OSPHOS treated horses had clinical signs of discomfort, nervousness, cramping, pawing, and/or colic immediately post-treatment. In 8 of the 10 horses, 10 to 15 minutes of hand walking resulted in resolution of clinical signs. One horse experiencing colic and hives required treatment with flunixin and dexamethasone to resolve clinical signs. In one other horse, clinical signs resolved without hand walking. Observations in 3 additional OSPHOS treated horses included lip licking, yawning, and/or head shaking. Adverse reactions occurring within 2 hours post-treatment with OSPHOS or the saline control are summarized in Table 4.

Table 4. Adverse Reactions Occurring Within 2 Hours Post-Treatment

Clinical Sign	OSPHOS (n=111)	Control (n=35)
Uncomfortable, Nervous, Colic, and/or Pawing	9.0% (10)	0% (0)
Lip licking	5.4% (6)	0% (0)
Yawning	4.5% (5)	0% (0)
Head Shaking	2.7% (3)	0% (0)
Injection Site Swelling	1.8% (2)	1 (2.9%)
Colic requiring treatment*	0.9% (1)	0% (0)
Hives/Pruritus	0.9% (1)	0% (0)

\* This horse experienced colic and hives and recovered after treatment with flunixin and dexamethasone.

The owner of one OSPHOS treated horse reported pawing and possibly rolling that occurred a day after treatment. The horse was normal on the day of treatment and the owner later believed this to be the normal behavior for the horse.

g. Conclusions:

This study demonstrates the effectiveness of OSPHOS for the control of clinical signs associated with navicular syndrome in horses. Adverse reactions associated with the administration of OSPHOS included discomfort, nervousness, pawing, colic, lip licking, yawning, head shaking, injection site swelling, and hives.

III. TARGET ANIMAL SAFETY:

A. Six Month Margin of Safety Laboratory Study:

1. Title: Evaluation of the margin of safety of intramuscularly administered clodronic acid (clodronate disodium) in horses. Study No.: CLR002
2. Study Dates: August 10, 2010 to January 28, 2011
3. Study Location:  
Johnson Research, LLC  
Parma, Idaho
4. Study Design:
  - a. *Objective*: To evaluate the safety of OSPHOS (60 mg/mL clodronate disodium) in horses when administered by intramuscular injection every 28 days for 6 months at dosages of 0 mg/kg (0X), 1.8 mg/kg (1X), 3.6 mg/kg (2X), and 5.4 mg/kg (3X) of body weight.
  - b. *Study Animals*: Thirty-two healthy horses of various breeds, geldings or intact, non-lactating, non-pregnant mares, 4 to 20 years of age, and weighing between 397-615.5 kg.
  - c. Treatment Groups and Drug Administration:

Table 1: Treatment Groups and Doses

Treatment Group	OSPHOS Dose	Number and Sex of Animals
0X (saline)	0 mg/kg	4 male, 4 female
1X	1.8 mg/kg	4 male, 4 female
2X	3.6 mg/kg	4 male, 4 female
3X	5.4 mg/kg	4 male, 4 female

Horses received 0X, 1X, 2X, or 3X the maximum recommended dose of OSPHOS by intramuscular injection every 28 days for a total of six administrations. Doses for all horses were split evenly into three injection sites. In cases where the total volume was greater than 45 mL (15 mL per site), the dose was split into four injection sites. Control horses were administered 0.9% Sodium Chloride at a volume equivalent to the 3X dose.

- d. *Inclusion/Exclusion Criteria*: Horses 4 years of age or older and in good to excellent health based on physical and clinical pathology findings were included.
- e. *Measurements and Observations*: General health observations were recorded twice daily. Concentrate consumption was recorded once daily. Body weights were measured pre-study and one day prior to each dose.

Physical examinations were conducted prior to inclusion, pre-treatment on all treatment days, and one day prior to study completion. Detailed post-treatment clinical observations were conducted at all treatment time points. Horses were evaluated continuously for 2 hours post-treatment, every 30 minutes through 6 hours post-treatment, hourly through 12 hours post-treatment, and at 24 hours post-treatment. Clinical pathology (hematology, coagulation, clinical chemistry) was evaluated pre-study, 24-hours post each treatment, and prior to necropsy. Additionally, blood urea nitrogen (BUN), creatinine, potassium, and ionized calcium concentrations were evaluated pre-study and at 1, 6, 12, 24, and 48 hours after each treatment, and prior to necropsy. Pharmacokinetic analysis was evaluated at Day 84; samples were collected prior to treatment, at 20 minutes, and 1, 3, 10, 24, and 48 hours post-treatment. Urinalysis was conducted pre-study, at Day 84, and prior to necropsy. Bone density (bone mineral content) was measured by radiographic photometry pre-study and prior to necropsy. Cortical bone strength (mechanical testing of cortical bone), gross necropsy, organ weights, and histopathology including bone marrow evaluation were evaluated post-mortem.

- f. *Statistical Analysis:* The study was conducted as a completely randomized design with a three-way treatment structure, dose with four levels (0X, 1X, 2X, and 3X), gender with two levels (gelding and mare), and time with the number of sampling events dependent on the response variable. In all analyses, the experimental unit was the individual animal. Differences were deemed significant if the p-value was < 0.10.

For continuous variables measured only once during the study (organ weights, organ weight relative to the final body weight, bone mineral content, and cortical bone strength variables), the data were analyzed using a linear model for a completely randomized design structure with a two-way treatment structure that included the fixed effects, treatment, gender, and the gender by treatment interaction.

For continuous variables measured more than once, the data were analyzed using a linear mixed model for a completely randomized design structure with repeated measures and a covariate. The fixed effects were treatment, gender, day, treatment by gender, gender by day, treatment by day, and treatment by gender by day. The pretreatment value nearest to the first day of treatment was used as the covariate. All analyses were conducted in SAS.

5. Results:

a. Post-Treatment Observations:

The most common post-treatment observations were clinical signs related to abdominal discomfort (colic). Signs of colic included rolling, full body stretching, repetitive lying down and rising, kicking at the abdomen, and other typical signs of acute abdominal discomfort. Horses exhibiting a single non-specific clinical sign such as pawing, pacing, agitation, or depression that did not also exhibit other signs indicative of abdominal discomfort were not included as cases of colic.

The incidence of colic was dose related. Over the course of the study, colic was observed following 94% (45/48) of 3X treatment administrations, 54% (26/48) of 2X treatment administrations, 4% (2/48) of 1X treatment administrations, and 8% (4/48) of 0X treatment administrations. Horses that appeared uncomfortable or that laid down and got up more than once were hand walked. Eighty percent (36/45) of the 3X horses, 31% (8/26) of 2X horses, and none of the 1X (0/2) and 0X (0/4) horses were hand walked due to colic. In the 3X group, clinical signs of colic often persisted after hand walking. Of the 36 3X treated horses that were hand walked, 19 horses required 2 to 4 episodes of hand walking. Clinical signs of colic developed shortly after treatment (ranging from 1 to 226 minutes) and resolved within 5.5 hours post-treatment.

Table 2. Colic by Treatment Group\*

Treatment Group	Incidence of Colic	Percent Colic	Number of Horses Walked	Number of Horses Walked More than Once
0X	4/48	8%	0	0
1X	2/48	4%	0	0
2X	26/48	54%	8	3
3X	45/48	94%	36	19

\*There were 8 horses per treatment group. Each horse was treated 6 times during the study for a total of 48 treatments per treatment group.

The following clinical signs were also commonly observed post-treatment: yawning, flehmen, tongue rolling, head shaking, and neck writhing. These clinical signs were observed in 50% (4/8) of 0X, 100% (8/8) of 1X, 88% (7/8) of 2X, and 100% (8/8) of 3X horses; see Table 3 for incidence of these signs by treatment administration.

Clinical signs including agitation, depression, pawing, and muscle fasciculations were also observed in a dose related manner. No horses in any treatment group received medical treatment other than hand walking, and all horses returned to normal within 5.5 hours post-treatment. Table 3 below describes the incidence of abnormal clinical signs by treatment group.

Table 3. Incidence of Abnormal Clinical Signs in the TAS Study

Clinical Sign	Number of Observations per Treatment Group (N=48 treatment administrations per group)			
	0X	1X	2X	3X
Colic*	4	2	26	45
Colic requiring hand walking	0	0	8	36
Yawning	5	17	16	30
Flehmen	0	0	8	2
Tongue Rolling	1	10	8	10
Head Shaking	1	5	3	7
Neck Writhing	0	0	0	6
Pawing	4	4	12	23
Agitation	1	1	7	10
Depression	0	2	5	21
Muscle Fasciculations/Trembling	0	0	1	4

\* Signs of colic included repeated lying down and rising, rolling, kicking at the abdomen, stretching of the abdomen and/or other typical signs of abdominal discomfort.

One 1X horse was noted to have mild facial nerve paralysis 28 minutes after the first dose of OSPHOS. The relationship of this finding to OSPHOS administration could not be determined because the facial nerve paralysis was difficult to detect on physical exam and appeared to resolve and then recur during the study.

b. Injection Sites:

Injection site reactions were identified in three 0X, four 1X, two 2X, and one 3X horse. One 1X horse had injection site reactions on two separate treatment days. Injection site reactions were characterized by soft or firm swellings and resolved within 10 days. In control horses, injection site swellings ranged from 0.5 cm diameter to 2 x 3 cm in size. In horses treated with OSPHOS, injection site swellings ranged from 0.5 cm diameter to 7 X 28 cm in size. Tissue from injection sites documented as injection site reactions were examined for gross and microscopic histology. Microscopic findings attributable to injection trauma occurred in all dose groups, including the 0X group.

c. Clinical Pathology:

Dose related trends were identified for blood urea nitrogen (BUN) and creatinine in horses administered OSPHOS. A statistically significant increase in the mean BUN concentration was observed in the 2X and 3X groups when compared to the 0X group on treatment administration Days 0, 28, 56, and 112. Mean BUN concentrations for the 3X group (up to 28 mg/dL) were slightly above the reference range (8-25 mg/dL) with many

individual animal concentrations above the reference range (up to 41 mg/dL).

Statistically significant higher mean creatinine concentrations were observed in the 3X group compared to the 0X group on three separate treatment administrations. Three 3X horses had creatinine concentrations above the reference range at 6 and/or 12 hours post-treatment after at least one treatment administration. Creatinine concentrations for these horses ranged from 2 to 2.5 mg/dL (reference range 0.9-1.9 mg/dL). All horses had creatinine concentrations within the reference range by 24 hours post-treatment.

One 3X horse had elevated BUN (up to 41 mg/dL) after all but the first administration of OSPHOS. This horse also had elevations in creatinine concentration at 6 to 12 hours after the final three administrations of OSPHOS. On Day 168 (28 days following the last administration of OSPHOS), the BUN concentration for this horse (28 mg/dL) remained above the reference range; however, the creatinine concentration was within the reference range and urine specific gravity at necropsy was within normal limits at 1.040.

Statistically significant increases in mean potassium concentrations were observed for the 2X and 3X treatment groups as compared to the control group on Days 84 and 140. Increases in potassium concentrations were observed within the first 6 hours post-treatment. Individual animal potassium concentrations were within the reference range with the exception of two 3X horses with post-treatment potassium concentrations up to 5.3 mg/dL (reference range: 3-5 mg/dL).

Elevated mean glucose concentrations were noted following all treatments in the 2X and 3X groups, and following the first treatment in the 1X group, compared to the control group.

Mean creatine kinase and aspartate aminotransferase concentrations were consistently increased post-treatment in OSPHOS treated groups as compared to the control group. All individual animal values returned to normal by the end of the study.

The mean chloride concentration was decreased for the 3X group as compared to the control group after all treatments and for the 2X group as compared to the control group after three of the treatments.

d. Gross Pathology and Histopathology:

Glandular gastric ulcers were identified in two 3X horses.

e. Bone Density and Bone Strength:

Bone density and bone strength were similar between OSPHOS treated and control groups.

f. Pharmacokinetics:

Blood samples were collected for pharmacokinetic analysis on Days 84 to 86 (after the third dose of a regimen consisting of a single IM injection administered once every 28 days) at the following times: prior to treatment (0), 20 minutes, and 1, 3, 10, 24, and 48 ( $\pm$  10 minutes) hours post-treatment. The plasma samples were analyzed for clodronic acid using Gas Chromatography/Mass Spectrometry (GC/MS). The mean  $\pm$  standard deviation results of the non-compartmental analysis are summarized in Table 4.

Table 4. Summary of Pharmacokinetic Parameters (Mean  $\pm$ SD)

Treatment Group	AUC <sub>0-LOQ</sub> (hr*mcg/mL)	C <sub>max</sub> (mcg/mL)	T <sub>1/2</sub> (hr)	T <sub>max</sub> (hr)	CL/F (mL/hr)
1X	12.15 $\pm$ 1.83	5.36 $\pm$ 0.98	1.65 $\pm$ 0.52	0.33 $\pm$ 0	0.12 $\pm$ 0.02
2X	22.85 $\pm$ 3.17	10.12 $\pm$ 0.90	2.04 $\pm$ 0.31	0.33 $\pm$ 0	0.12 $\pm$ 0.03
3X	62.49 $\pm$ 18.52	15.22 $\pm$ 1.84	2.89 $\pm$ 1.33	0.50 $\pm$ 0.31	0.08 $\pm$ 0.02

AUC<sub>0-LOQ</sub> = area under the concentration 0 hr to last quantifiable concentration

C<sub>max</sub> = maximum concentration

T<sub>1/2</sub> = plasma elimination half-life

T<sub>max</sub> = time of maximum concentration

CL = Total systemic clearance

F = Fraction absorbed

SD = standard deviation

Clodronic acid was rapidly absorbed from the intramuscular administration sites, with a short plasma half-life, ranging from 1.65 to 2.89 hours. The maximum concentration (C<sub>max</sub>) increased in proportion to dose, which is consistent with the rapid and dose proportional absorption and lack of drug accumulation in the plasma following repeated doses at 28 day intervals. There were dose proportional increases in the AUC when single and multiple doses up to 2X were administered, but there was a greater than dose proportional increase in the AUC when multiple 3X doses were administered. It is concluded that this change was due to an apparent decrease in CL/F (p=0.001). This decrease in CL/F also led to an increase in T<sub>1/2</sub> at the 3X dose. Upon examining the shape of the concentration-time profiles, it was determined that the change in CL/F was not attributable to a saturable elimination process, but rather to a possible decrease in renal clearance in the presence of repeated exposure at the 3X dose.

6. Conclusion: This study supports the safe use of OSPHOS when administered at a dose of 1.8 mg/kg to healthy horses. Clinical signs associated with administration of OSPHOS included colic, agitation, and mild neurologic signs, such as tongue rolling and head shaking, that resolved within 5.5 hours following administration. Clinical pathology abnormalities associated with administration of OSPHOS included elevations in serum BUN, creatinine, glucose, and potassium concentrations and decreases in serum chloride concentrations.

B. NSAID and 5X Laboratory Safety Study

1. Title: A two-phase, pilot, safety study evaluating the use of intramuscular clodronate disodium solution in horses concurrently receiving oral phenylbutazone and the safety of intramuscular clodronate disodium solution in horses at 5X the recommended maximum dose. Study No.: CLR004
2. Study Dates: July 2009 to August 2009
3. Study Location:  
 Johnson Research, LLC  
 Parma, Idaho
4. Study Design:
  - a. *Objective*: To evaluate the safety of OSPHOS when administered at the recommended dose rate of 1.8 mg/kg (1X) via intramuscular injection in horses concurrently receiving oral phenylbutazone (Phase I); and to evaluate the safety of intramuscular OSPHOS when administered to horses at 5X the recommended dose of 1.8 mg/kg (Phase II).
  - b. *Study Animals*: Six healthy grade or Appaloosa horses, geldings or intact, non-lactating, non-pregnant mares, 4 to 15 years of age, and weighing between 386-553 kg.
  - c. Treatment Groups and Drug Administration:

Table 5: Treatment Groups and Doses

Phase	OSPHOS	Phenylbutazone	Number and Sex of Animals
I	1.8 mg/kg on Day 4 (1X) (maximum dose 900 mg)	4.4 mg/kg BID Day 0-3 2.2 mg/kg BID Day 4-6	3 male, 3 female
II	9 mg/kg on Day 22 (5X) (maximum dose 4500 mg)	NA	3 male, 3 female

This study was conducted with a single treatment group. Horses were administered the final formulation of OSPHOS containing 60 mg clodronate disodium per mL and a commercially available phenylbutazone paste.

Phase I: On Days 0 to 3, horses were orally administered 4.4 mg/kg phenylbutazone twice a day (maximum daily dose of 4 g per day). On Day 4, horses were administered 1.8 mg/kg (1X) OSPHOS (maximum dose of 900 mg) by intramuscular injection divided evenly into three injection sites. On Days 4 to 6, horses received 2.2 mg/kg phenylbutazone orally twice a day (maximum daily dose of 2 g per day).

Phase II: On Day 22, horses were administered 9 mg/kg (5X) OSPHOS (maximum dose of 4500 mg) by intramuscular injection divided evenly into 5 injection sites.

- d. *Inclusion/Exclusion Criteria*: Healthy horses 4 years of age or older were included.
- e. *Measurements and Observations*: Body weight, food consumption, clinical observations, physical examination, and clinical pathology (hematology, coagulation and clinical chemistry) were performed. Additionally, blood samples from all animals were assayed for urea nitrogen, creatinine, and ionized calcium at 6 and 12 hours post-treatment in each Phase of the study.
- f. *Statistical Analysis*: This study consisted of one group of 6 horses, each completing two separate study phases (Phase I and II). In all analyses, the experimental unit was the individual animal. Differences were deemed significant if the p-value was < 0.10.

For continuous variables measured only once during the study or outcomes where 5 or fewer result categories were observed, data were evaluated using a generalized linear mixed model assuming a multinomial distribution and a cumulative logit link.

For continuous variables measured repeatedly throughout the study, the data were analyzed using a linear mixed model for repeated measures with the fixed effects time, gender, and the time-by-gender interaction. All analyses were conducted in SAS.

#### 5. Phase I Results:

##### a. Post-Treatment Observations:

Three horses at 24 hours post-treatment had an excited attitude and two of these horses had with an elevated pulse rate of 60 beats per minute.

##### b. Injection Site Observations:

No injection site reactions occurred during Phase I.

##### c. Clinical Pathology:

At 24 and 48 hours post-treatment, the mean concentration for BUN was statistically elevated compared to the mean concentration prior to treatment. One horse had elevated BUN concentrations (24 hrs: 33 mg/dL; 48 hrs: 42 mg/dL) above the reference range (8-25 mg/dL) when OSPHOS was administered concurrently with phenylbutazone treatment. BUN concentrations for the other horses remained within the reference range. Creatinine concentrations were within the reference range for all horses.

Mean concentrations for sodium, chloride, and magnesium were decreased, and the mean glucose concentration was increased at 24 and 48 hours post-treatment compared to immediately prior to treatment.

6. Phase II Results:

a. Post-Treatment Observations:

Within 6 minutes of administration of OSPHOS at 9.0 mg/kg (5X), 5 out of 6 horses developed changes in attitude associated with signs of agitation or nervousness including pawing, circling, and tail twitching. In the same time frame, 4 out of 6 horses developed non-specific signs including excessive yawning, flehmen, tongue rolling, head shaking, and head bobbing. All 6 horses developed mild to moderate muscle fasciculations between 2 and 30 minutes post-treatment. By 30 minutes post-treatment, 4 out of 6 horses also developed signs of discomfort and abdominal pain including full body stretching, repetitive lying down, and kicking at the abdomen. Three out of 6 horses developed temporary gait abnormalities that included mild to moderate hypermetria and spasticity, and in one case also included mild ataxia.

One horse displayed signs of acute abdominal pain within 8 minutes post-treatment. At approximately one hour post-treatment this horse exhibited excessive agitation along with the colic signs and developed acute ileus by 2 hours post-treatment. The horse responded to medical therapy and was clinically normal at 7 hours post-treatment.

b. Injection Site Observations:

One horse developed swelling at an injection site 24 hours post-treatment.

c. Clinical Pathology:

At 24 and 48 hours following administration of 5X the recommended OSPHOS dose, the mean concentration for BUN was statistically significantly elevated compared to the mean BUN concentration immediately prior to treatment. Four individual horses had BUN concentrations above the reference range post-treatment (ranging from 26 to 33 mg/dL; reference range 8-25 mg/dL). Mean concentrations for creatinine exhibited a statistically significant increase at 24 and 48 hours post-treatment compared to immediately prior to treatment. One horse had creatinine concentrations above the reference range at 6 and 12 hours post-treatment (2.0 mg/dL; reference range 0.9-1.9 mg/dL). Post-treatment creatinine concentrations were higher than pre-treatment concentrations for all horses (increases from pre-treatment concentration of 0.3-1.0 mg/dL). Mean concentrations for creatine kinase also exhibited a statistically significant increase at 24 and 48 hours post-treatment compared to immediately prior to treatment.

7. Conclusions:

Concurrent administration of phenylbutazone at the recommended dose of OSPHOS resulted in a trend towards increasing BUN concentrations.

At 5X the recommended dose of OSPHOS, test article related effects included colic and neurologic clinical signs. One horse required medical treatment for colic, which took 7 hours to resolve. Neurologic signs included hypermetria,

spasticity, and ataxia. Clinical pathology abnormalities associated with a 5X dose of OSPHOS included elevations in BUN and creatinine.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in horses. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

The product labeling contains the following Warning statement: Do not use in horses intended for human consumption.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to OSPHOS:

Not for use in humans. Keep this and all drugs out of reach of children. Consult a physician in case of accidental human exposure.

VI. 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. The data demonstrate that OSPHOS, when used according to the label, is safe and effective for the control of clinical signs associated with navicular syndrome in horses.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is needed in the diagnosis and treatment of navicular syndrome in horses, and for monitoring for possible adverse reactions of the drug.

B. Exclusivity:

OSPHOS, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act because this is the first time we are approving this active ingredient in a new animal drug.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.