Date of Approval: December 20, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-559

Zycosan™

(pentosan polysulfate sodium injection)

Injectable Solution

Horses

For the control of clinical signs associated with osteoarthritis in horses.

Sponsored by:

Anzac Animal Health, LLC

Executive Summary

Zycosan™ (pentosan polysulfate sodium injection) is approved for the control of clinical signs associated with osteoarthritis in horses.

Safety and Effectiveness

The sponsor conducted a field study in client-owned horses that had unilateral lameness with diagnosed osteoarthritis in the lame limb. Enrolled horses were non-pregnant mares, geldings, and stallions with a range of ages, weights, and breeds. Horses in the treatment group received Zycosan™ by intramuscular (IM) injection in the neck once every 7 days for 4 weeks for a total of 4 doses. Horses in the control group were given an equal volume of saline at the same dosage regimen.

Each horse's lameness was graded on Days 0 and 28 of the study. On Day 28, more horses in the Zycosan™ treated group had improved lameness grades compared to the control group and the study results indicated that treatment with Zycosan™ at the labeled dose benefited horses with single limb lameness due to osteoarthritis.

The most common adverse reactions associated with the administration of Zycosan™ were injection site reactions (pain, heat, swelling, redness, and neck muscle cramping) and prolonged coagulation parameters (activated partial thromboplastin time (aPTT) and prothrombin time (PT)). Some injection site reactions initially occurred around the time of dosing (peri-dosing) and other injection site reactions were initially delayed (up to 3 days after dosing). All peri-dosing reactions resolved without specific treatment. All delayed reactions resolved within 5 days from onset, and most did not require treatment. Clinical signs of bleeding or thrombocytopenia were not seen in any horses.

The sponsor conducted a laboratory safety study in healthy geldings and non-pregnant mares (ages 3- to 7-years-old) to evaluate the toxicity of Zycosan™ when given IM at 0X, 1X, 3X, and 5X the labeled dose of 3 mg/kg for 12 weeks (3X the labeled duration). All horses were dosed by IM injection once weekly for 12 consecutive weeks following the initial dose for a total of 13 doses. Horses in the 0X group were given an equal volume of saline as the 5X group at the same dosage regimen.

The administration of Zycosan™ resulted in injection site reactions (pain and swelling) and prolonged coagulation parameters (aPTT and PT). Horses also had abnormal gross pathology and histopathological findings at the injection site. Zycosan™-treated horses in all dose groups had a dose-dependent increase in aPTT within 6 hours of dosing. The aPTT returned to normal in the 1X group within 24 hours but remained elevated at 24-hours post-dosing in the 5X group. Horses with prolonged coagulation times did not show signs of coagulopathy.

Other Safety Information

Because pentosan polysulfate sodium is a weak anticoagulant, people who take an anticoagulant should use caution when handling or administering Zycosan™.

Conclusions

Based on the data submitted by the sponsor for the approval of Zycosan™, FDA determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-559

B. Sponsor

Anzac Animal Health, LLC
218 Millwell Dr.
Suite B
Maryland Heights, MO 63043

Drug Labeler Code: 086073

C. Proprietary Name

Zycosan™

D. Drug Product Established Name

pentosan polysulfate sodium injection

E. Pharmacological Category

Low molecular weight heparin-like compound

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

250 mg/ml

H. How Supplied

7.5 ml single use vial

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Administer 3 mg/kg (1.4 mg/lb) by intramuscular injection once weekly for four weeks (for a total of four doses). Zycosan™ is provided in a single use vial and does not contain a preservative. **Discard unused vial contents.**

K. Route of Administration

Intramuscular injection

L. Species/Class

Horses

M. Indication

For the control of clinical signs associated with osteoarthritis in horses.

II. EFFECTIVENESS

The effectiveness of Zycosan™ for the control of clinical signs associated with osteoarthritis in horses was demonstrated in one well-controlled field study described below. This study demonstrated that Zycosan™ is effective for the control of clinical signs associated with osteoarthritis in horses.

A. Dosage Characterization

There are several pentosan polysulfate products authorized for use in horses in other countries. The dosage chosen to be confirmed in the field effectiveness study for Zycosan™ (3 mg/kg once weekly for four weeks) was based on the recommended dose on labeling of products authorized for use in other countries, as well as data from one peer-reviewed, published study conducted in the United States. The peer-reviewed study used a different formulation of pentosan polysulfate sodium than that of Zycosan™.

The peer-reviewed U.S. study evaluated pentosan polysulfate sodium in 18 horses in an induced carpal joint osteoarthritis model.[1] Nine horses received pentosan polysulfate sodium at 3 mg/kg intramuscularly (IM) on study days 15, 22, 29, and 36 (post-operatively), while the other nine received saline. Clinical signs (lameness, carpal flexion, and joint effusion), radiographs, and coagulation parameters were evaluated along with gross, histologic, histochemical, biochemical, and synovial fluid analysis of joint tissues and/or fluids. There were no differences in the clinical, radiographic, or gross pathology parameters between treatment groups. However, the study authors concluded that administration of pentosan polysulfate sodium may have had beneficial effects on the synovial fluid and the articular cartilage.

B. Substantial Evidence

1. Clinical Field Study

   Title: Clinical Field Study to Evaluate Injectable Pentosan Polysulfate for the Control of Clinical Signs Associated with Osteoarthritis in Horses. (Study No. OA-AZ-1801)

   Study Dates: July 23, 2019 to March 08, 2022

   Study Locations:

Exeter, CA	Boone, IA
Brandon, FL	Arthur, IL
Ocala, FL	Plympton, MA
Wellington, FL	Browns Summit, NC

[1] McIlwraith CW, Frisbie DD, and Kawcak CE. Evaluation of intramuscularly administered sodium pentosan polysulfate for treatment of experimentally induced osteoarthritis in horses. *Am J Vet Res*. 2012 May; 73 (5): 628-33.

Apollo, PA
Quakertown, PA
Anderson, SC
Ridgefield, WA

Study Design:

Objective: To evaluate the effectiveness of Zycosan™ in controlling the clinical signs associated with osteoarthritis in horses.

Study Animals: Two hundred and thirty-seven client-owned horses (82 non-pregnant/non-lactating mares, 151 geldings, and 4 stallions), aged 3-32 years old, of various breeds, and weighing between 153-904 kg (337 to 1989 pounds) were enrolled in the study. One hundred and twenty horses received Zycosan™ and 117 horses received a volume matched negative (saline) control. Horses had unilateral lameness between Grade 2 and 4 (≥ 2 and ≤ 4) according to the American Association of Equine Practitioners (AAEP) Lameness Scale (see below under Measurements and Observations). Osteoarthritis was diagnosed in the lame (index) limb, as confirmed by radiographs performed prior to enrollment (Day -5 to Day 0). Nerve blocks were also permitted to confirm and localize the clinical lameness.

Horses with prior diagnosis of bleeding issues (including exercise induced pulmonary hemorrhage), or those where trauma or bleeding were expected to occur during the study time-period (e.g., from planned surgery) were not enrolled. Horses receiving systemic non-steroidal anti-inflammatory drugs at the start of the study were not enrolled.

Experimental Design: The study was a negative controlled, randomized, masked, multi-site field study designed to evaluate the field safety and effectiveness of Zycosan™ for the control of clinical signs associated with osteoarthritis in horses when injected intramuscularly at 3 mg/kg (1.4 mg/lb) once every seven days for four doses (4 weeks). Masking was maintained via separation of functions. Clinical investigators responsible for clinical assessments were masked to treatment. Each study site had a treatment administrator that was unmasked to treatment assignments and was responsible for preparing and administering the treatment for individual horses away from any masked study personnel including the clinical investigator and owner/caretaker. The study was conducted in accordance with Good Clinical Practice (GCP) principles.

Drug Administration: Study horses were administered 3 mg/kg (1.4 mg/lb) Zycosan™ or an equal volume of saline by intramuscular injection in the neck once every seven days (study days 0, 7, 14, and 21) for four doses (4 weeks). Treatment group information is displayed in Table II.1.

Table II.1: Treatment Groups

Treatment Group	Dose	Number of Horses Enrolled and Included in Safety Population (N = 237)	Number of Evaluable Horses Included in Effectiveness Population (N = 222)
Zycosan™	3 mg/kg	120	109
Negative Control (Saline)	0 mg/kg	117	113

Measurements and Observations:

Radiographs were obtained on study day 0 (or up to 5 days prior to study day 0) to confirm osteoarthritis in the affected limb (index limb) and on study day 28. Physical exams and lameness assessments were performed prior to treatment at each study visit (study days 0, 7, 14, 21, and 28). Lameness and physical examinations were also performed if a horse was removed from the study and at the discretion of the clinical investigator at any unplanned visits.

Lameness was evaluated at a walk, straight line trot, and circling to the left and right. An AAEP lameness grade was assigned as follows:

0: Lameness not perceptible under any circumstances.
1: Lameness is difficult to observe and is not consistently apparent, regardless of circumstances (e.g., under saddle, circling, inclines, hard surface, etc.).
2: Lameness is difficult to observe at a walk or when trotting in a straight line but consistently apparent under certain circumstances (e.g., weight-carrying, circling, inclines, hard surface, etc.).
3: Lameness is consistently observable at a trot under all circumstances.
4: Lameness is obvious at a walk.
5: Lameness produces minimal weight bearing in motion and/or at rest or a complete inability to move.

Injection site observations were performed by the clinical investigator prior to treatment and then again 3 hours post-treatment on study days 0, 7, 14, and 21. These observations specifically assessed for the presence of swelling (edema), heat, pain, and redness at the injection site. Treatment administrators also evaluated horses for reactions at the time of injection on study days 0, 7, 14, and 21.

Blood and serum samples were collected prior to treatment for clinical pathology (hematology and serum chemistry) on study days 0, 14, and 28. Clinical pathology may also have been performed on other study days at the discretion of the clinical investigator (e.g., in response to an adverse event). Blood samples were also collected both pre-treatment and 3 hours post-treatment on study days 0, 14, and 21 to evaluate coagulation parameters (aPTT and PT).

Horses were monitored for adverse events by the clinical investigator and the horse owner/caretaker throughout the study. Horse owners/caretakers

observed horses daily between treatment days and through the end of the study (study day 28) to monitor for injection site reactions, attitude, appetite, drinking habits, and manure quality/quantity. A follow-up phone call to the owner/caretaker was also performed after the treatment period concluded (study day 38).

Statistical Methods: Effectiveness was assessed at study day 28. The experimental unit was the individual horse. Horses were considered a treatment success if the baseline lameness grade (study day 0) in the index limb improved by ≥ 1 AAEP lameness grade on Day 28. Any horses that were withdrawn from the study for perceived ineffectiveness or failure to improve, or at any time for treatment-related reasons, were classified as treatment failures. The results from all evaluable cases were analyzed using the generalized linear mixed effect model (GLIMMIX) procedure in Statistical Analysis Software (SAS). Treatment was included in the model as a fixed effect and site and the treatment by site interaction were included as random effects. A logit link function was employed in the model because the variable is binary in nature. Statistical significance was evaluated at a two-sided alpha equal to 0.05.

Results: All treated horses were included in the field safety analysis. Two hundred and twenty-two horses (109 Zycosan™ and 113 saline control) were included in the evaluation of effectiveness (final effectiveness analysis).

The treatment success rate was 57% for horses in the Zycosan™ group and 36% in the negative control group. The difference in the success rates between the two treatments was not statistically significant ($p = 0.0548$). The point estimates of the treatment success rate indicate a clinically relevant effect size. Sensitivity analyses showed that due to variability across sites, the statistical significance of the results varied depending on the inclusion of a small number of cases ($n = 3$). The persuasive size of the effect in the larger proportion of the study supports the conclusion that this field study demonstrated substantial evidence of effectiveness. Treatment success rates are show in Table II.2.

Table II.2: Day 28 Treatment Success Rates

Treatment Group	Number of Horses	Percent Success
Zycosan™	109	57%
Negative Control (Saline)	113	36%

Adverse Reactions: Injection site reactions were the most frequently reported adverse reactions during the study. Injection site reactions were associated with clinicopathology changes in some cases. Other adverse reactions reported in more than one horse included prolongation of coagulation parameters (aPTT and PT), lethargy, behavior changes, and colic. Adverse reactions are summarized in Table II.3. Horses may have experienced more than one of the observed adverse reactions.

Table II.3: Adverse Reactions

Adverse Reaction	Number (%) of Zycosan™ Treated Horses (N = 120)	Number (%) of Saline Treated Horses (N = 117)
Immediate or Peri-Dosing Injection Site Reaction*	21 (18%)	4 (3%)
Delayed Injection Site Reaction$^{\Delta}$	13 (11%)	3 (3%)
Prolonged aPTT (post-treatment)	18 (15%)	1 (1%)
Prolonged PT (post-treatment)	5 (4%)	1 (1%)
Lethargy	14 (12%)	7 (6%)
Behavior Change$^{€}$	10 (8%)	8 (7%)
Colic	2 (2%)	0 (0%)
Elevated Sorbitol Dehydrogenase (SDH)	1 (1%)	0 (0%)
Stiffness	1 (1%)	0 (0%)

*Occurring 0-3 hours post-injection; observed clinical signs included pain, heat, swelling, edema, redness, or neck muscle cramping. Horses may have experienced more than one episode.

$^{\Delta}$ Occurring more than 3 hours post-injection; observations included pain, heat, swelling, edema, redness, or neck muscle cramping. Pain may have been exhibited local to the injection site and as reluctance to eat, drink, or move the neck or head. Horses may have experienced more than one episode.

$^{€}$ Observations included aggression, stomping, pawing, agitation, anxiousness, overactivity, quietness and/or depression, or unsettledness.

Injection Site Reactions:
Injection site reactions (heat, pain, swelling/edema, or redness) occurred more frequently and were generally more severe in Zycosan™ treated horses as compared to control horses over the course of the study.

Injection site reactions in Zycosan™ treated horses were predominantly characterized by swelling/edema ranging in size from 0.2 cm to 15 cm at their widest point. Pain was the most commonly observed concurrent clinical sign associated with the swelling/edema in Zycosan™ treated horses. Pain may have been exhibited local to the injection site and as reluctance to eat, drink, or move the neck or head. Lethargy or depression was also reported concurrently in some horses. One Zycosan™ treated horse had muscle cramping observed concurrently.

One Zycosan™ treated horse with a peri-dosing injection site reaction showed concurrent clinically relevant prolongation of both aPTT and PT post-treatment on study day 14. There were no clinical signs of bleeding in this horse. Seven Zycosan™ treated horses exhibited peri-dosing injection site reactions after more than one treatment timepoint. Peri-dosing injection site reactions in Zycosan™ treated horses occurred most often following the first (11 occurrences), second (7 occurrences), or third injection (8 occurrences). Three Zycosan™ treated horses with peri-dosing injection site reactions

displayed sustained swelling, pain, or edema for up to three days post-injection. All peri-dosing injection site reactions resolved without specific treatment.

Delayed injection site reactions in Zycosan™ treated horses were initially observed greater than 3 hours and up to 3 days post-injection. All delayed injection site reactions in Zycosan™ treated horses resolved within 5 days from onset and most did not require treatment. Two Zycosan™ treated horses experienced multiple occurrences of delayed injection site reactions during the study with one horse exhibiting swelling, pain, or heat following each of the four injections. One Zycosan™ treated horse with a delayed injection site reaction experienced a small swelling accompanied by heat and pain. This horse also concurrently developed mild hyperglycemia and an increase in its white blood cell count and neutrophilia. This horse recovered without treatment. Two Zycosan™ treated horses experienced more severe clinical signs 1-2 days following the second injection. These horses both exhibited a 15 cm plaque of edema (at the widest point) accompanied by pain and heat at the injection site. One of the horses was also noted to be reluctant to move its head or neck and to have a slightly elevated respiratory rate the day following injection. The other affected horse showed concurrent clinical signs of anorexia, depression, and fever. At the time of the observed injection site reaction, both horses showed mild hyperbilirubinemia, mild hyperglycemia, mild neutrophilia, and mild monocytosis on clinical pathology. Both the Zycosan™ treated horses with more severe clinical signs were removed from the study and treated with flunixin meglumine. The Zycosan™ treated horse with concurrent fever was also treated with an oral antibiotic for 5 days. Both horses recovered within 5 days from the onset of clinical signs.

Coagulation Parameters:
Increases in post-treatment mean values for aPTT were observed at all timepoints in the Zycosan™ treated group. Mean post-treatment aPTT values increased by approximately 19 seconds for the Zycosan™ treated group at each timepoint but remained within the reference range. Similar increases were not observed in control horses.

Clinically relevant prolongation of aPTT values occurred post-treatment in 18 Zycosan™ treated horses, with some horses experiencing prolongation of aPTT at multiple timepoints. Clinically relevant prolongation in PT occurred post-treatment in 5 Zycosan™ treated horses. Three Zycosan™ treated horses showed concurrent clinically relevant prolongation of aPTT and PT at study day 0 (N = 1) or study day 14 (N = 2). One of the horses with post-treatment prolongation of aPTT and PT at study day 14 was concurrently reported to have an injection site reaction.

Clinical signs of bleeding or thrombocytopenia were not observed in any horses.

Colic:
Two Zycosan™ treated horses developed clinical signs of colic (lethargy, generalized discomfort, decreased appetite, decreased water intake, and/or decreased manure output) within 12 hours following treatment after the third injection. One horse was diagnosed with a pelvic flexure impaction. This horse

was not noted to display any outward clinical signs of injection reaction preceding the colic episode. The other horse was noted to display a markedly lowered head position prior to the colic diagnosis. In both cases the colic resolved within 24 hours with symptomatic treatment (single nasogastric intubation with osmotic agents/fluids). The horse with the lowered head position also received a single intravenous treatment with detomidine hydrochloride and flunixin meglumine.

Hepatic System:
One Zycosan™ treated horse had an increase in SDH in conjunction with trending increases in aspartate aminotransferase (AST) and alanine transaminase (ALT) that did not exceed the reference range. γ-glutamyl transferase (GGT) values for this horse were in the high normal range prior to treatment. Changes in GGT were not observed after treatment. Concurrent clinical signs were not observed in this horse.

Conclusions: This study demonstrates the effectiveness of Zycosan™ for the control of clinical signs associated with osteoarthritis in horses. Zycosan™ had an acceptable safety profile in the target population. Adverse reactions associated with the administration of Zycosan™ included injection site reactions (pain, heat, swelling, or redness), prolongation of coagulation parameters (aPTT and PT), lethargy, behavior changes, colic, stiffness, and increased SDH. Injection site reactions were associated with fever, depression or lethargy, tachypnea, hyperglycemia, and elevated bilirubin values and leukocytes in some cases.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: A 12 Week Evaluation of the Safety of Pentosan Polysulfate Sodium in Horses. (Study No. 017-01611)

Study Dates: June 1, 2018 to June 23, 2020

Study Location: Las Cruces, NM

Study Design:

Objective: To evaluate the margin of safety of Zycosan™ administered by intramuscular injection to horses once per week at 0X, 1X, 3X, and 5X the maximum exposure dose for 12 weeks.

Study Animals: 32 horses (16 non-pregnant mares and 16 geldings) of various breeds, 3 to 7 years of age, and weighing between 427 and 541 kg, were enrolled in the study. Enrolled horses were in good health based on physical examination and clinical pathology findings and had a temperament amenable to treatment.

Experimental Design: The study was conducted in accordance with Good Laboratory Practices (GLP). Enrolled horses were randomized by sex to one of

four treatment groups and randomly assigned to stall and treatment order within sex.

Table III.1: Treatment Groups

Treatment Group	Treatment	Dose mg/kg (Multiple of Labeled Dose)	Number and Sex of Animals
1	Negative control (Saline)	0 mg/kg (0X)	4 male/4 female
2	Zycosan™	3 mg/kg (1X)	4 male/4 female
3	Zycosan™	9 mg/kg (3X)	4 male/4 female
4	Zycosan™	15 mg/kg (5X)	4 male/4 female

Drug Administration: The test and control articles were administered by injection in the muscle of the neck. Horses in Groups 2 to 4 were administered the appropriate dose based on current body weight, once weekly for 13 doses. Group 1 (saline control) horses were dosed with a volume equivalent to the Group 4 (5X) horses. For doses greater than 20 ml, the calculated volume was divided between the left and right neck musculature. The side of the neck used for test article administration was alternated each week. Horses were observed at 2, 4, and 6 hours post-dose for injection site reactions or adverse events.

Measurements and Observations: Twice daily observations, daily feed consumption, physical examinations (performed pre-dose and post-dosing on dosing days), body weight, injection site observations (performed on all animals at 2, 4, and 6 hours post-dose and daily until resolution), adverse event monitoring, hematology and coagulation, serum biochemistry, urinalysis, and full gross and microscopic pathology.

Statistical Methods: The experimental unit was defined as the individual animal. Summary statistics (mean, standard deviation, minimum, maximum, and number of animals) for males and females within each treatment group at each study day/time-point were calculated for all quantitative variables. Continuous variables measured at multiple times during the study (body weight, physical examination outcomes, clinical pathology, and food consumption) were analyzed by a repeated measures analysis of covariance (RMANCOVA), with treatment, sex, time, treatment-by-sex, sex-by-time, treatment-by-time, and treatment-by-sex-by-time in the model as fixed effects, and animal identified as the subject in the repeated statement. When variables were measured at unequally spaced intervals (coagulation outcomes), the covariance structure in the repeated measures analysis was investigated using three structural assumptions: compound symmetry (CS), CS heterogeneous (CSH), and spatial power [SP(POW)]. When variables were measured at equally spaced intervals, the covariance structure in the repeated measures analysis was investigated using four structural assumptions: CS, CSH, first order autoregressive [Ar(1)], and heterogeneous first order autoregressive [ARH(1)]. Continuous variables measured only once during the study (absolute organ weights and the organ weight to body weight ratio) were analyzed by an analysis of variance (ANOVA), with treatment, sex, and treatment-by-sex interaction in the model as fixed effects. All statistical tests and pairwise comparisons between treatment groups were based on a significance level of 0.10 except for three-way interactions, which were tested at a significance level of 0.05.

Results: All horses were dosed intramuscularly once weekly for 12 consecutive weeks following the initial dose (13 total doses). Increased coagulation parameters and abnormal injection site findings (found on gross necropsy and histopathology) were the most common treatment-related findings.

Injection Site Assessment: The most common post-treatment observations were pain and swelling (edema) at the injection site. Injection site inflammation was evaluated qualitatively by visual observation and palpation, and quantitatively by measuring lesion dimensions. Swelling and pain were noted in the Zycosan™ treated horses at 2, 4, and 6-hours post-dose in the 1X, 3X, and 5X dose groups but had a higher incidence in the 3X and 5X dose groups. The average injection site reaction lasted between 2-6 days in the 5X group; 0-4 days in the 3X group; and 0-2 days in the 1X group. At study day 21 (after 4 doses), 5/8 of the 1X group horses were noted to have an injection site reaction, 5/8 of the 3X group horses and all 5X group horses (8/8) had injection site reactions consisting of pain and swelling. By study day 63 (10 doses) 6/8 of the 1X group horses had an injection site reaction. At 6 hours post-injection, swellings in all dose groups ranged from 0.25 inches to 8 inches in diameter. One 5X horse had an injection site reaction of greater than 8 inches in diameter on study day 49. Horses in the saline control group also were noted to have swelling and pain post injection, with the most occurrences of injection site reaction at study day 21 (3/8).

One 3X horse experienced decreased appetite and lethargy after the fourth injection of Zycosan™. This horse was administered one dose of oral electrolyte paste and two doses of flunixin meglumine for muscle pain and dehydration. This horse was also noted to be holding her head low and had muscle spasms at 6 hours post injection. One 5X horse developed swelling on his ventral thorax at study day 84.

Clinical Pathology:
Coagulation Parameters
Administration of Zycosan™ was associated with a dose-dependent increase in aPTT in all horses administered Zycosan™. No horses developed clinical signs of coagulopathy. On study day 0, at 6- and 24-hours post-administration, aPTT values were significantly higher in the 3X and 5X dose groups when compared to the saline control group. At 6 hours post-injection, aPTT values in the 3X group ranged from 48.8 to 103.5 seconds (laboratory reference range 28-44 seconds) and from 118 to 170.2 seconds in the 5X group. At 24 hours post injection, aPTT values ranged from 41.6 to 44.6 seconds in the 3X group and 49 to 76.9 seconds in the 5X group. At 24 hours post-injection, the 1X group horses had aPTT values within the laboratory reference range.

On Days 28 and 56 at 6 hours post injection of Zycosan™, aPTT values had a more than 4-fold prolongation, with values greater than 190 seconds (the upper limit of the laboratory reference range) in all 5X group horses and one horse in the 3X dose group. Horses in the 3X dose group had at least a 2-fold prolongation compared with pre-dose values, with values ranging from 60.9 to 190 seconds at 6-hours post-administration on study day 28 and with values ranging from 67.3 to 165.4 seconds at 6-hours post-administration on study day 56. Minimally prolonged aPTT, as compared with Day -7 pre-dose value, was noted in all horses in the 1X dose group at the 6-hours post-dose time point on study days 0, 28, and 56 (average values ranged from 38.9 to 48.9 seconds).

Prolongation of aPTT in the 1X dose group was considered treatment-related because most of the aPTT values at the 6-hours post-dose time point exceeded the upper limit of the reference range and a consistent group effect was noted.

Figure III.1: Group average Activated Partial thromboplastin time (aPTT)

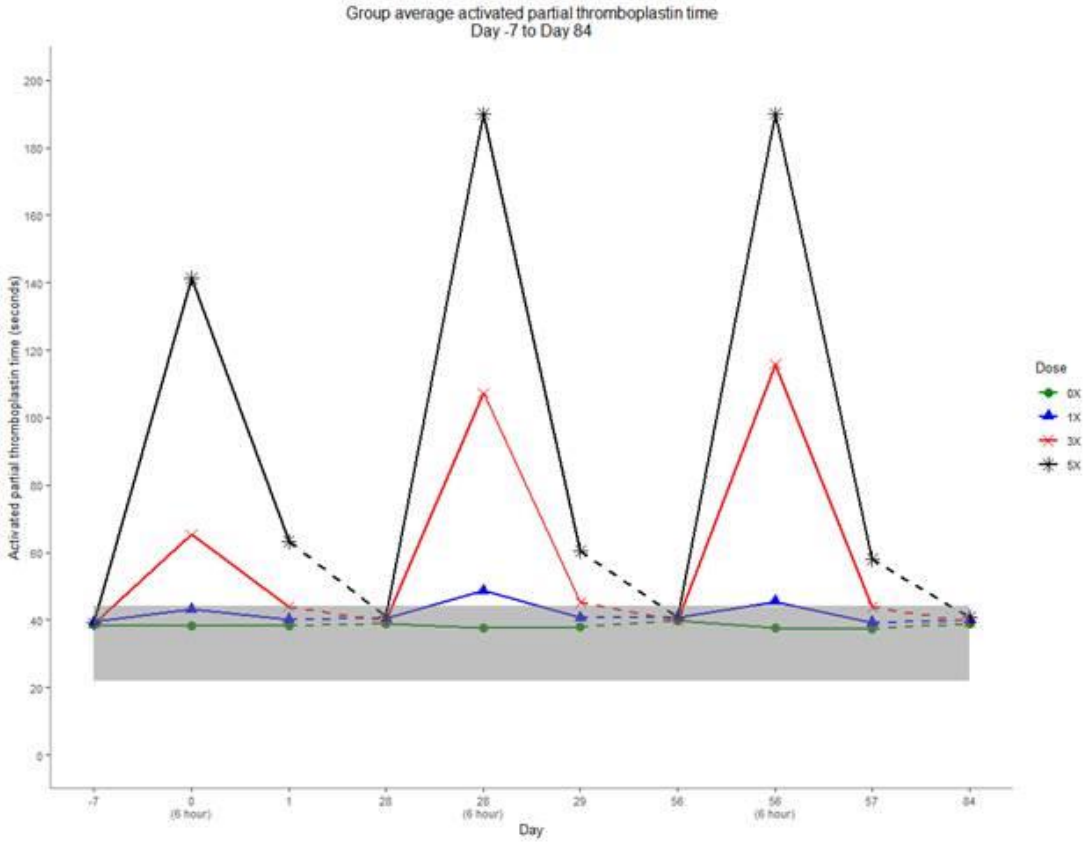

Figure III.1 illustrates the dose-dependent prolongation of the mean aPTT values in horses in the different treatment groups. The colored lines and marks represent the dose groups. The x-axis along the bottom of the graph represents the study days, and the y-axis represents the mean value of aPTT (measured in seconds). The gray shaded area in the graph represents the normal reference range of aPTT (28-44 seconds) in horses for the clinical pathology laboratory. The upper limit of the laboratory reportable range was 190 seconds. The actual peak values of aPTT shown in the graph above may be higher. The black line with the asterisk represents the 5X group horses, the red line with the "x" mark represents the 3X group horses, the blue line with the triangle represents the 1X group horses, and the green line with the dot represents the control (0X) horses. At 6 hours post injection, all horses administered Zycosan™ showed a dose-dependent prolongation of aPTT. The aPTT values were trending back toward the reference range at 24-hours post-dose. Coagulation parameters were not evaluated for each weekly dose; therefore, it is unclear at what time point the aPTT returned to the normal reference range between 24 hours post-injection and the subsequent measurement of aPTT.

Prothrombin Time was prolonged at 6 hours post-dose administration in the 5X dose group when compared to baseline and remained prolonged at 24 hours post-dose. Two 5X group horses continued to have additional mild increases in PT

by 0.4-0.5 seconds at 24 hours post-dose relative to 6 hours post-dose. The majority of PT values for horses in all groups remained within the laboratory reference range.

Clinical Chemistry
Mean GGT values in the 5X dose group were significantly higher than values in the 0X group. GGT values in all horses stayed within the laboratory reference range.

Mean SDH values in the 5X dose group were significantly higher than values in the 0X dose group. All values except three horses in the 5X dose group were within the laboratory reference range of 2.0-6.0 mg/dL. One horse had an SDH value of 6.1 mg/dL measured after 9 and 13 doses, respectively; one horse had a value of 8.4 mg/dL after 13 doses; and one horse had one elevated SDH value of 6.8 mg/dL after 5 doses. No horses had clinical signs of hepatic disfunction.

Gross Pathology and Histopathology:
Injection sites
Hemorrhage and congestion in the interstitium/subcutis at the injection site was noted in horses in all Zycosan™ treated groups and was associated with the infiltration of pigmented macrophages; however, the magnitude tended to be greater in horses in the 5X group. These findings correlated with macroscopic observations of discoloration of fascial planes, discoloration of adjacent fascia and/or subcutis, and fluid along fascial planes or within the subcutis. Yellow pigment deposits within injection sites were noted in horses in the 3X and 5X groups, which was associated with mild fibrosis and perivascular inflammation of mononuclear or mixed cells. Fibrosis and discoloration of the interstitium occurred in all Zycosan™ treated groups with increased severity in 3X and 5X groups.

Liver
Liver to body weight ratios were increased when comparing the 5X group to the control horses. However, absolute liver weights were not increased and there were no histopathologic changes noted upon examination of the liver.

Conclusion: This study supports the safe use of Zycosan™ at the dose of 3 mg/kg given intramuscularly once weekly for 4 doses. Zycosan™ administration was associated with a dose dependent increase in aPTT within 6 hours of dosing in all dose groups. The aPTT returned to normal in the 1X group within 24 hours; however, aPTT remained elevated at 24 hours post-dosing in the 5X group. No horses exhibited signs of coagulopathy. Other treatment related effects included pain and swelling at the injection site.

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 Zycosan™:

Not for use in humans. Keep out of reach of children. Pentosan polysulfate sodium is a weak anticoagulant. Caution should be used when administering Zycosan™ if you are taking an anticoagulant. **In case of accidental self-injection, seek immediate medical attention**. **If product comes into contact with skin, rinse skin thoroughly with water and seek medical attention if needed.** To obtain a Safety Data Sheet (SDS), contact Dechra at (866) 933-2472.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Zycosan™, when used according to the label, is safe and effective for the control of clinical signs associated with osteoarthritis in horses.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to diagnose osteoarthritis, properly administer the injection, and monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

Zycosan™, 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 FD&C Act because this is the first time we are approving this active moiety in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.