Date of Approval: November 25, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-513

Zimeta™

dipyrone injection

Horses

For the control of pyrexia in horses

Sponsored by:

Kindred Biosciences, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-513

B. Sponsor

Kindred Biosciences, Inc.
1555 Bayshore Hwy.
Suite 200
Burlingame, CA 94010

Drug Labeler Code: 86078

C. Proprietary Name

Zimeta™

D. Product Established Name

Dipyrone Injection

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Sterile solution

G. Amount of Active Ingredient

500 mg dipyrone per mL

H. How Supplied

Zimeta™ (dipyrone injection) is available as a 500mg/mL sterile solution in a 100mL multi-dose vial.

I. Dispensing Status

Rx

J. Dosage Regimen

Zimeta™ is administered by intravenous injection, once to twice daily for up to three days, at a dosage of 30 mg/kg (13.6 mg/lb). The overall duration of treatment with Zimeta™ is dependent on the response observed (fever reduction). Zimeta™ may be re-administered based on recurrence of fever for up to 3 days at 12 hour intervals.

K. Route of Administration

Intravenous injection

L. Species/Class

Horses

M. Indication

Zimeta™ (dipyrone injection) is indicated for the control of pyrexia in horses.

II. EFFECTIVENESS

A. Dosage Characterization

The dose of dipyrone injection was selected based on published literature and drug products containing dipyrone approved in foreign markets, and two pilot laboratory effectiveness studies. The findings of the pilot laboratory studies are summarized below.

In the first laboratory study, 8 adult horses, ages 3 years to 20 years, with naturally occurring pyrexia (rectal temperature ≥102.0°F) received an intravenous injection of dipyrone at a dosage of 30 mg/kg. Rectal temperature was measured at six hours post-dosing to determine effectiveness. Responders were defined as having a rectal temperature that either decreased by ≥2.0°F or had returned to normal (≤101.0°F). Six out of eight horses were considered responders. Following the determination of effectiveness, horses continued to be monitored for pyrexia over the duration of the study (Day 0 - Day 4). Horses were eligible to be re-dosed with dipyrone if pyrexia (rectal temperature of ≥102.0°F) was documented. Repeated dosing was allowed at any interval greater than 8 hours. The number of treatments administered to individual horses during the duration of the study ranged from 1 to 6. Five out of eight study horses received additional doses of dipyrone; each of these 5 horses received a total of 6 doses of dipyrone during the study and 3 of these horses received 3 doses of dipyrone within a 24-hour time period.

In the second laboratory study, 31 adult horses, ages 3 years to 20 years, with naturally occurring pyrexia (rectal temperature ≥102.0°F) received a single intravenous injection of dipyrone at a dose of 30 mg/kg (N=15) or placebo control (saline) at an equal volume (N=16). Rectal temperature was measured at six hours post-dosing to determine effectiveness. Twenty-four to thirty hours following the first dose, horses that had another febrile episode (27 horses) crossed over to the other treatment arm and received either a single intravenous injection of dipyrone at a dose of 30 mg/kg (N=14) or placebo control (saline) at an equal volume (N=13). Responders were defined as having a rectal temperature six hours after dosing that decreased by ≥2.0°F or had returned to normal (≤101.0°F). Following the first dose, 10 of 15 horses treated with dipyrone were responders, and 2 of 16 horses treated with placebo control were responders. After the second dose, 8 of 14 horses treated with dipyrone were responders, and 0 of 13 horses treated with placebo control were responders. All horses were treated with a maximum of one dose of dipyrone, and one dose of the placebo control during the study.

B. Substantial Evidence

1. Type of Study: Clinical Field Study

Title: A multicenter, prospective, randomized, controlled clinical trial to assess the effectiveness and field safety of metamizole sodium (dipyrone) for the control of pyrexia in horses. Study No.: KB0120

Study Dates: April 22, 2015 to Oct 25, 2015

Study Locations: Fourteen clinical investigation sites from the following locations enrolled horses in the study.

Sallisaw, OK
Nampa, ID
Georgetown, KY
Lodi, WI
Weatherford, TX
Peyton, CO
Aubrey, TX
Purcell, OK
Apollo, PA
Clermont, FL
Las Vegas, NV
Rockwood, TN
Snohomish, WA
Farmerville, LA

Study Design: The field study was divided into two phases; an effectiveness phase (Study day 0, hour 0 through hour 6) and an extended use field safety phase. The effectiveness phase was a randomized, masked, controlled, multicenter, field study to investigate the effectiveness of Zimeta™ (dipyrone injection) in controlling pyrexia in horses. The extended use field safety phase was an open-label (no control product was administered), single arm, multi-dose, field study to evaluate the safety of Zimeta™ (dipyrone injection) when administered intravenously at 30 mg/kg bodyweight to horses with pyrexia. Horses that responded to treatment (dipyrone injection or control product) in the effectiveness phase were eligible to enroll in the extended use field safety phase of the study after the effectiveness phase was complete (hour 6) and could remain in this phase for the duration of the study. The total duration of the extended use field safety phase was decreased from 5 days to 3 days after the study was initiated.

Objective: The study objective was to evaluate the effectiveness and field safety of Zimeta™ (dipyrone injection) at a dose of 30 mg/kg body weight for the control of pyrexia in horses with naturally-occurring disease.

Study Animals: One hundred and thirty-eight horses of various breeds were enrolled in the study. Horses were enrolled with fever due to a variety of underlying diseases including bacterial and viral respiratory infection, musculoskeletal infection, gastro-intestinal infection, and immune-mediated disease. Seventy-four of the enrolled horses were client owned horses and the remaining enrolled horses were purpose bought horses. Horses ranged in age from 1 to 32 years of age and weighed between 159 and 800 kilograms. Multiple

pure and mixed breed horses were represented, with the majority of horses characterized as Quarter Horse, Paint, Thoroughbred, Arabian, and crossbred. There were 19 stallions, 45 geldings, and 74 mares enrolled. 138 horses received treatment (104 Zimeta™ and 34 control product) and 137 horses (103 Zimeta™ and 34 control product) were included in the statistical analysis for effectiveness. A total of 107 horses received at least one dose of Zimeta™ (dipyrone injection) during the effectiveness or extended use field safety phases of the field study, including 3 horses originally assigned to the control product group.

Treatment Groups: During the effectiveness phase, horses were randomly assigned to two treatment groups in a 3:1 ratio of Zimeta™ or control product. The control product was a vehicle control (formulation minus active ingredient) with additional ingredients added to maintain masking during administration. Effectiveness was assessed at 6 hours following initial treatment administration (hour 6 on day 0).

Table II.1: Treatment Groups During the Effectiveness Phase (study day 0, hours 0 through 6)

Treatment Group	Dose	Number of Horses Enrolled (evaluable)
Zimeta™ (dipyrone injection)	30 mg/kg	104 (103)
Control Product	0 mg/kg	34 (34)

Drug Administration: In the effectiveness phase, horses were administered 30 mg/kg Zimeta™, or an equal volume of control product, by intravenous injection once on study day 0. Upon completion of the effectiveness phase, horses that were considered a treatment success and exhibited an additional febrile event (56 Zimeta™ treated horses and 3 control horses) continued to the extended use field safety phase where they were administered at least one additional dose of Zimeta™ dosed at 30 mg/kg by intravenous injection. Repeated dosing was allowed at any interval of 8 hours or greater. The majority of horses in the extended use field safety phase were treated once per day with Zimeta™. No horses in the extended use field safety phase were treated with Zimeta™ more than twice daily. The total duration of treatment for each individual horse was dependent on the clinical response observed and the underlying disease process in the horse.

Measurements and Observations: Each horse was given a complete physical examination by a veterinarian and assessed for pyrexia at enrollment (day 0) and 6 hours following initial treatment administration (day 0, hour 6). If horses enrolled in the extended use field safety phase of the study, additional rectal temperature measurements were performed until study exit. Horses receiving any additional doses of Zimeta™ during the extended use field safety phase were monitored for adverse reactions; however, no additional effectiveness data were collected on these horses.

Blood samples for hematology, chemistry, and coagulation determinations were collected prior to treatment and at study exit. Three to seven days following study exit, any new adverse events that occurred following treatment were reported to the veterinarian.

Rectal temperature: Rectal temperature was measured on day 0 (hour 0) and again 6 hours following the initial treatment administration. Effectiveness was assessed on day 0 at hour 6. Horses were considered a treatment success if they displayed a ≥2.0°F decrease in rectal temperature or a return to normothermia (rectal temperature ≤101.0°F) at hour 6.

Statistical Methods: The individual horse served as the experimental unit. Superiority of Zimeta™ over the control product was established by a statistically-significant difference between the proportion of successes in the Zimeta™ and control groups, and a higher success rate in the Zimeta™ group compared to the control group. Treatment effect was tested using Fisher's exact test, with a two-sided alpha = 0.05 (the FREQ procedure in SAS®, SAS Institute, Cary NC, version 9.4).

Results: At hour 6 of the study, 77 of the 103 Zimeta™ treated horses, and 7 out of 34 control horses were treatment successes. The difference in success rate was statistically significant at P<0.0001, as shown in Table II.2 below.

Table II.2. Effectiveness at Hour 6 Post-Treatment

Treatment Group	Zimeta™ (dipyrone injection) N=103	Control Product N=34
Number of Success (%)	77 (74.8%)	7 (20.6%)
95% Confidence Interval	(65.2%, 82.8%)	(8.7%, 37.9%)
P-value†	<0.0001	

† P-value is from Fisher's exact test

Adverse Reactions: Adverse reactions reported during the field study (effectiveness phase or extended use field safety phase) are summarized in Table II.3. Horses may have experienced more than one of the observed adverse reactions during the field study. Horses may have received a single dose of Zimeta™ or multiple doses of Zimeta™ during the field study.

Table II.3: Adverse Reactions Reported During the Field Study with Zimeta™

Adverse Reaction	Zimeta™ (dipyrone injection) (N=107)	Control Product (N=31)
Elevated Serum Sorbitol Dehydrogenase (SDH)	5 (5%)	5 (16%)
Hypoalbuminemia	3 (3%)	1 (3%)
Gastric Ulcers	2 (2%)	0 (0%)
Hyperemic Mucosa Right Dorsal Colon	1 (1%)	0 (0%)
Prolonged Activated Partial Thromboplastin Time (APTT)	1 (1%)	0 (0%)
Elevated Creatinine	1(1%)	0 (0%)
Injection Site Reaction	1 (1%)	0 (0%)
Anorexia	1 (1%)	1 (3%)

Horses with elevated SDH, hypoalbuminemia, prolonged APTT, or elevated creatinine did not show associated clinical signs. One horse exhibited an exacerbation of pre-existing hypoalbuminemia after treatment; this horse also showed concurrent elevation in SDH. Two horses that received Zimeta™ were diagnosed with gastric ulcers. One horse that received 4 doses of Zimeta™ was diagnosed with grade III/IV gastric ulceration and hyperemia of the mucosa of the right dorsal colon on post-mortem examination which was performed following euthanasia due to illness unrelated to treatment (septic arthritis and cellulitis). This horse was previously treated with a different NSAID prior to enrollment in the study. A second horse that enrolled in the study due to a mandibular facial wound and received two doses of Zimeta™ was diagnosed with grade III/IV gastric ulcers 4 days following completion of the field study.

In the field study, Zimeta™ was used concomitantly with other therapies, including antibiotics and sedatives.

Conclusions: The results of this study demonstrate that Zimeta™ (dipyrone injection) is effective at 6 hours post-dosing for the control of pyrexia in horses. Field safety data from this study support the safe use of Zimeta™ (dipyrone injection) when administered at 30 mg/kg intravenously once or twice daily, for up to three days.

III. TARGET ANIMAL SAFETY

The safety of Zimeta™ was evaluated in the three laboratory studies (KB0124, KB0122, KB-012-TAS-011) outlined below and the field effectiveness study (KB0120) outlined above under Substantial Evidence of Effectiveness. A dosing frequency of Zimeta™ given three times daily (every eight hours) did not demonstrate an adequate margin of safety due to concerns related to the treatment-related prolongation of coagulation test results (PT and APTT values), and clinical signs of coagulopathy in some study horses. Study KB0122, which evaluated the safety of three times daily dosing of Zimeta™, also revealed dose-dependent effects on the

liver (increase in liver weights and total serum bilirubin). Additionally, moderate to severe infectious lower respiratory disease in many horses in study KB0122 complicated interpretation of study results. Study KB0124 was a pilot effectiveness study in horses with pyrexia and study KB-012-TAS-011 was a laboratory safety study that evaluated the safety of administration of Zimeta™ at two and three times daily dosing intervals.

The absence of coagulopathy in the twice daily treatment groups supports the conclusion that there is an adequate margin of safety when dipyrone injection is administered at the label dose up to twice daily (every 12 hours). The adverse reactions from the field study are reported above; results from the field study reveal that dosing with the label dose at once or twice daily intervals was not associated with clinical coagulopathy in the target animal population. In addition, the overall results from the safety studies support the conclusion that the respiratory disease, and the severity of clinical signs of respiratory disease, observed in study KB0122 was not likely related to the administration of dipyrone injection.

Overall safety of Zimeta™ was evaluated by comparing the safety data from the three laboratory studies and the field effectiveness study. A comparison of the coagulation data reported in each study, in combination with the absence of clinical signs of coagulopathy in studies KB0120 and KB-012-TAS-011, demonstrated that Zimeta™ (dipyrone injection) is safe when administered at 30 mg/kg IV not more frequently than every 12 hours for up to 3 days.

A. Pilot Laboratory Study:

A pilot laboratory study (KB0124) was conducted in 31 adult horses, ages 3 years to 20 years, with naturally occurring fever (due to respiratory disease or other infectious process) to evaluate the effectiveness of a non-final market formulation of dipyrone injection at a dose of 30 mg/kg intravenously. One horse developed soft feces after treatment with one dose of dipyrone injection and a second horse developed bloody nasal discharge and died one day after receiving one dose of dipyrone injection. Necropsy findings for the horse that died documented severe pleuropneumonia; however, due to the potential effects of dipyrone on platelet aggregation and function, the occurrence of bloody nasal discharge and progression of disease in this horse may be related to treatment. There were no substantive differences between the non-final market formulation used in this pilot study and Zimeta™ (dipyrone injection).

B. Nine Day Margin of Safety Laboratory Study:

Title: Evaluation of the margin of safety of intravenously administered metamizole sodium [dipyrone injection] in horses. Study Number: KB0122.

Study Dates: August 2015-March 2016

Study Location: Parma, Idaho

Study Design:
Objective: To evaluate the margin of safety of Zimeta™ (dipyrone injection) when administered intravenously to horses for 9 days at doses of 0 mg/kg (0X), 30

mg/kg (1X), 60 mg/kg (2X), and 90 mg/kg (3X) three times daily. The study was conducted under Good Laboratory Practices (GLP).

Study Animals: 41 horses were obtained from a single source. 32 horses (16 non-pregnant mares and 16 geldings) were selected from this initial pool of candidates and enrolled. Candidate horses were to be in good health based on physical and clinical pathology findings prior to enrollment. Enrolled animals represented various breeds, were 3 to approximately 18 years of age, and weighed 370-568 kg. Enrolled horses were verified culture negative for *Streptococcus equi* subspecies *equi* by nasal lavage prior to enrollment. Gastroscopy was performed during acclimation, prior to Day -14. Due to the presence of gastric lesions, all candidate horses were administered oral omeprazole (GastroGard®, Merial Ltd) during acclimation at 4 mg/kg once daily for 8 to 11 days depending on block assignment. Some horses were ultimately excluded from enrollment due to the severity of gastric ulceration prior to study initiation.

Experimental Design: The selected horses were randomized to pens. A block randomization procedure was used to assign horses to treatment (See Table III.4). Blocks were formed based on the location of pens. Due to time and facility constraints, necropsies were performed on only 8 horses per day. Therefore, each block constituted a necropsy group and was randomly assigned to necropsy groups 1 to 4, and study activities were staggered by one day for each necropsy group. Masking was maintained by separation of function. Individuals without knowledge of treatment group assignments performed all clinical observations, veterinary physical examinations, clinical pathology sample analyses, and macroscopic pathology examinations. Individuals involved in dosing the animals with test article had knowledge of treatment assignment and therefore did not assist in other aspects of the study.

Table III.4. Treatment Groups

Treatment Group	Dose mg/kg (multiple of labeled dose)	Number and Gender of Animals
1 (saline control)	0 mg/kg (0X)	4 male/4 female
2	30 mg/kg dipyrone injection (1X)	4 male/4 female
3	60 mg/kg dipyrone injection (2X)	4 male/4 female
4	90 mg/kg dipyrone injection (3X)	4 male/4 female

Drug Administration: Intravenous (IV) catheters were placed in the jugular vein of each horse for administration of the test article. Catheters were replaced as needed during the study, but at least one time for each horse. Test article was administered by intravenous catheter according to assigned treatment group every 8 hours for 9 consecutive days. Control horses were administered 0.9% sodium chloride at a volume equivalent to Treatment Group 4 (3X).

Measurements and Observations: General health observations were recorded twice daily. Feed concentrate consumption was recorded once daily, and water consumption twice daily. Body weights and physical examinations were measured pre-study (during acclimation and again Day -1), mid-study (Day 4), and prior to necropsy (Day 8). Clinical pathology (hematology, coagulation, clinical chemistry) was evaluated pre-study (Day -1 or 0, prior to treatment), mid-study (Day 2-4), and prior to necropsy (Day 8). Urinalysis was conducted pre-study (Days -6 to -4), mid-study (Days 2 or 3), and at necropsy.

During the necropsies, diagnostic microbiology samples were also collected for analysis, at the discretion of the pathologist. For select horses with evidence of lung pathology on necropsy, samples were submitted to a separate diagnostic laboratory to be tested with a diagnostic PCR equine respiratory disease pathogen panel that detects DNA from influenza A (H3N8), equine rhinitis A, equine rhinitis B, EHV-1, EHV-1 neuropathogenic, EHV-1 non-neuropathogenic, EHV-4, and *Streptococcus equi* subspecies *equi*. Other samples were submitted for standard bacterial culture.

Statistical Methods: In all analyses, the experimental unit was the individual animal. All tests were performed at 0.10 level of significance.

For continuous variables measured only once during the study (organ weights and organ weight relative to the final body weight), analysis of variance (ANOVA) with treatment, sex, and treatment by sex interaction as the fixed effects was used to test for differences among treatment groups. If treatment by sex interaction was significant, pair-wise comparisons of each treatment group versus placebo using linear contrasts were performed within sex. If treatment-by-sex interaction was not significant and treatment main effect was significant, pair-wise comparison of each treatment group versus placebo for pooled gender were performed.

For continuous variables measured more than once (serum chemistry, coagulation, hematology, urinalysis, body weight, body temperature, heart rate and respiratory rate), repeated measures analysis of covariance was used to test for differences among treatment groups. The model included treatment, time, sex, and all interactions as fixed effects. Time was modeled as a repeated factor, with animal as the subject of repeated measurements. The covariance structure was either compound symmetry or heterogeneous compound symmetry, based on the minimum Akaike information criterion (AIC). In addition, baseline values were included as a covariate regardless of its significance. Baseline values were defined as the values prior to and nearest to the first dosing.

Results:

Clinical Observations

The most common post-treatment observations were clinical signs associated with infectious respiratory disease. During the course of the study respiratory disease was identified in multiple horses, and lung pathology was confirmed at necropsy. The most common abnormal observations included cough, depression, tachypnea or dyspnea, epistaxis, nasal discharge, inappetence, and fever (Table III.5). Multiple pathogens were identified by culture at necropsy, and the most severely affected animals appeared to be in the dipyrone treated groups. However, animals in the control group were also affected by respiratory disease and lung pathology on necropsy, and therefore the respiratory disease is not likely related to treatment with dipyrone. However, it is not clear if dipyrone treatment worsened the clinical signs of respiratory disease in the dipyrone treated groups.

There were also several jugular vein complications, such as thrombophlebitis, that were determined to be related to the IV catheter, and not related to treatment with dipyrone.

Table III.5. Number of Horses with Abnormal Observations*

Abnormal Observation	Number of Horses in Control Group	Number of Horses in 1X Group	Number of Horses in 2X Group	Number of Horses in 3X Group
Depression	2	2	3	3
Anorexia or decrease appetite	1	2	3	3
Cough	0	1	2	2
Tachypnea and/or Dyspnea	0	1	1	2
Nasal Discharge	0	1	2	2
Fever (T>101.5°F)	1	2	0	1
Epistaxis	0	0	0	2
Hives	0	1	0	1
Loose Feces	0	2	0	1
Colic**	0	0	2	1
Edema of head/neck	0	0	2	1
Death	0	0	0	1

*Some horses had several of the same observation over the course of the study, and some observations were made only once
**Including recumbence associated with other signs of discomfort, rolling, or pawing

One horse in the 3X group with severe clinical signs associated with pneumonia spontaneously died prior to completion of the study. This horse had observations of epistaxis for 46 hours with increasing dyspnea and discomfort, prior to spontaneous death at Day 7. Microbiologic culture from necropsy samples revealed *Staphylococcus aureus*. This horse had associated prolongations in both prothrombin time (PT) and activated partial thromboplastin time (APTT) (see Clinical Pathology) on Day 4; these parameters were not measured again prior to death.

Another horse in the 3X group had observed nasal discharge with epistaxis that resolved prior to study completion. This horse also had other clinical signs and necropsy findings consistent with coagulopathy including: hemorrhage from previous catheter site, renal abscessation and hemorrhage, and petechial and ecchymotic hemorrhage of the ileum. This horse had associated prolongations in both PT and APTT (see Clinical Pathology) on Day 8.

Clinical Pathology

Coagulation Times
Prothrombin time (PT) was statistically significantly prolonged for the 2X and 3X dose groups when compared to controls (overall p=0.0037). While not statistically significant, the 1X group trended towards increases over control as well (see Table 6). Two 3X horses with the largest prolongations of PT, also had considerable prolongations of activated partial thromboplastin time (APTT), in addition to clinical signs of coagulopathy.

Table III.6. Summary of Prothrombin Time Effects

Treatment Group	Prothrombin Time – Least Squares Mean	P-value
Group 1 (0X control)	12.734	NA
Group 2 (1X)	13.374	0.276
Group 3 (2X)	14.524	0.005
Group 4 (3X)	14.946	0.001

Activated partial thromboplastin time (APTT) was not statistically different between groups. The laboratory reference range provided was 28 to 44 seconds. Several horses in all treatment groups had values above the reference range provided; however, only 2 of the 3X horses had clinical signs of coagulopathy. See Table III.7.

Table III.7. Summary of Activated Partial Thromboplastin Time Effects

Treatment Group	Number of Values Above the reference range on Day 8 (>44 seconds)	Individual Observed Values Above the reference range on Day 8 (seconds)
Group 1 (0X control)	1/8	45.7
Group 2 (1X)	1/8	46.7
Group 3 (2X)	3/8	47, 49.9, 51.1
Group 4 (3X)	3/7*	45.3, 47.9, 51.4

*One 3X horse died prior to Day 8, this horse's APTT value at Day 4 was the highest recorded in the study, at 59.1 seconds, and is not included in this table.

Total Bilirubin
Horses in the 2X and 3X treatment groups had dose-dependent elevations in total bilirubin midway through the study and dose-dependent elevations with mean values above the reference range at study termination. These elevations appear to be related to treatment with Zimeta™ and associated with increased liver weights on necropsy. These findings were not associated with clinical signs or liver pathology. There were no clinically relevant or statistically significant elevations in other enzymes associated with liver dysfunction or hepatocellular damage, including aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP).

Sorbitol dehydrogenase
There were no statistically significant differences in SDH in treated groups versus control. In the control group, one horse had a value above the reference range at Day 4 (7.5 U/L, reference range 0.5-6.0 U/L), which was decreased from the baseline value. In the 1X group, one horse had a significantly elevated SDH at Day 8, with a value of 30.7 U/L. No other 1X horses had values outside of the reference range. In the 2X group, 3 horses had values slightly above the reference range on Day 8 (6.5, 8.7, and 9.0 U/L). In the 3X group, 2 horses had values above the reference range at Day 4 (6.7 and 7.1 U/L), and one had a value above the reference range at Day 8 (9.0 U/L). These elevations were not associated with liver pathology at necropsy.

Gross Pathology and Histopathology

Gastrointestinal

On necropsy, duodenal erosion was present in one 3X horse. Stomach (non-glandular) erosions were present in one control horse and two 1X horses. Stomach (non-glandular) ulcers were present in one control horse and one 2X horse. No erosions or ulcerations were identified in the large intestine.

Renal

There were three 1X horses, two 2X horses, and three 3X horses with minimal or mild renal tubular dilation. Renal tubular dilation was not present in any control animal. One 1X horse and two 3X horses had renal tubular mineralization. There were no control horses with renal tubular mineralization. These histopathology changes were all classified as minimal or mild by the pathologist and were not associated with changes in clinical pathology (blood urea nitrogen (BUN) and creatinine values in all treatment groups remained within the normal reference range) or clinical signs of renal dysfunction.

Hepatic

A statistically significant difference (p=0.0323), dose-dependent increase in liver weight was observed in the 2X and 3X treatment groups.

Histopathologic changes in the liver were identified in all treatment groups, including the control group. All pathologic findings were classified as minimal or mild by the pathologist, except one control horse with moderate fibrosis. There was no significant liver pathology and no dose response in the mild pathology present. The hyperbilirubinemia and increased liver weights were not associated with liver pathology.

Conclusions: Zimeta™ (dipyrone injection) administration was associated with dose-dependent increases in liver weights, total serum bilirubin, and prolonged prothrombin time. Two horses in the highest dose group (3X) demonstrated clinical signs of coagulopathy, associated with prolonged prothrombin times and activated partial thromboplastin times. Additionally, moderate to severe infectious lower respiratory disease in many horses complicated interpretation of study results. This study does not demonstrate an adequate margin of safety when Zimeta™ (dipyrone injection) is administered three times daily.

C. Nine Day Coagulation and Pharmacokinetic Laboratory Study:

Title: Evaluation of Coagulation and Pharmacokinetics of Intravenously Administered Dipyrone in Horses. Study number KB-012-TAS-011.

Study Dates: November-December 2016

Study Location: Parma, Idaho

Study Design:

Objective: To evaluate the effects of Zimeta™ on coagulation parameters and pharmacokinetic parameters when administered intravenously to horses for 9 days at doses of 0 mg/kg (0X) twice daily (BID), 30 mg/kg (1X) BID, 60 mg/kg (2X) BID, 90 mg/kg (3X) BID, 30mg/kg (1X) three times daily (TID), and 60mg/kg (2X) TID.

Study Animals: Thirty-two healthy horses, 16 males (geldings) and 16 females (mares) who were non-pregnant and non-lactating. Enrolled horses were of various breeds, were between 3 years and 20 years of age, and weighed 388-627 kg. All horses were in good health based on physical and clinical pathology findings prior to enrollment. Enrolled horses were verified to be culture negative for *Streptococcus equi* subspecies *equi* by nasal lavage.

Experimental Design: The selected horses were randomized to pens and then to treatment group (See Table III.8) using incomplete block design. Blocks were formed on the location of pens. Individuals without knowledge of treatment group assignments performed all clinical observations, veterinary physical examinations, and clinical pathology sample analyses. Individuals involved in dosing the animals with test article had knowledge of treatment assignment and therefore did not assist in other aspects of the study.

Table III.8. Treatment Groups

Treatment Group	Dose mg/kg (multiple of labeled dose)	Frequency	Number and Gender of Animals
1 (negative control)	0 mg/kg (0X)	Twice daily	2 males/2 females
2	30 mg/kg dipyrone injection (1X)	Twice daily	3 males/3 females
3	60 mg/kg dipyrone injection (2X)	Twice daily	3 males/3 females
4	90 mg/kg dipyrone injection (3X)	Twice daily	3 males/3 females
5	30 mg/kg dipyrone injection (1X)	Three times daily	2 males/2 females
6	60 mg/kg dipyrone injection (2X)	Three times daily	3 males/ 3 females

Drug Administration: Zimeta™ was administered by intravenous catheter according to assigned treatment group every 8 (TID) or 12 hours (BID) for 9 consecutive days. Control horses were administered 0.9% sodium chloride twice daily at a volume equivalent to Treatment Group 2 (1X).

Measurements and Observations: General health observations were recorded twice daily. Feed concentrate and water consumption were recorded once daily. Body weights and physical examinations were measured pre-study and at the conclusion of the study (Day -8, Day -4, Day -1 and Day 10). Clinical pathology (hematology and coagulation) was evaluated pre-study (Day -1 or 0, prior to treatment), mid-study (Day 2-4), and at study conclusion (Day 10). Serum chemistry was collected on Day -8 only. Blood samples for pharmacokinetic evaluation were collected throughout the treatment period.

Statistical Methods: In all analyses, the experimental unit was the individual animal. All tests were performed at 0.1 level of significance.

For continuous variables measured only once during the study [area under the curve (AUC) for the treatment period], ANOVA was used to evaluate differences

between the treated groups. The model included treatment, sex, and treatment-by-sex interaction as fixed effects. The control group was not included in the analysis. If treatment by sex interaction was significant, pair-wise comparisons between the treated groups were performed for each individual sex. If treatment-by-sex interaction was not significant and treatment main effect was significant, pair-wise comparison between the treated groups for pooled gender were performed.

For continuous variables measured more than once (coagulation), repeated measures analysis of covariance was used to evaluate the treatment effect on the coagulation variables. The model included treatment, time, sex, and all interactions as fixed effects, and block as random effect. Time was modeled as a repeated factor, with animal as the subject of repeated measurements. The covariance structure was either compound symmetry or heterogeneous compound symmetry, based on the minimum Akaike information criterion (AIC). In addition, baseline values were included as a covariate regardless of its significance. Baseline values were defined as the values prior to and nearest to the first dosing.

Results: All horses survived to study conclusion.

Clinical Observations: The most common treatment-related adverse effects were anorexia, depression, and loose feces. Seven horses in Zimeta™ treated groups experienced one or more of these adverse effects, as compared to no horses in the control (0X) group. One horse in the 2X TID group had varying degrees of depression, loose feces, and colic for multiple days during the study which resolved with hand-walking. At completion of study, the study horses were healthy when returned to the source herd.

Coagulation Parameters
Prothrombin Time (PT)
There was an upward numerical trend in the PT which suggested a treatment effect of dipyrone on prolongation of PT, although the overall treatment effect for PT was not significant (P=0.1131). Based on the prolongations in PT seen in Study KB0122, pairwise contrasts between the control group and each treated group were conducted, which showed that the 3X BID group had significantly different (and prolonged) PT compared to the control group (P=0.0014). Additionally, the horses with the largest increases over baseline values (at least 10% increase) were in the 2X TID group (2/6 horses) and 3X BID group (3/6 horses).

Activated partial thromboplastin time (APTT)
Horses in all treatment groups, including the control group, had increases in APTT of 10 to 20% over baseline values. No significant differences were detected among groups (p=0.9287).

Pharmacokinetics:
Blood samples were collected for pharmacokinetic analysis (see Table 9 for sampling time points) throughout the treatment period and were measured for the active metabolite of dipyrone, 4-MAA, using a validated liquid chromatography-mass spectrometry (LC/MS/MS) method.

Table III.9: Blood collection time points (in hours) for pharmacokinetic analysis by group

Group	Day 1	Day2	Day 4	Day 6	Day 8	Day 9
1X BID	0, 0.25, 1, 4, 8, 12	Trough	Trough	Trough	Trough	0, 0.25, 1, 4, 8, 12
1X TID	0, 0.25, 1, 4, 8	Trough	Trough	Trough	Trough	0, 0.25, 1, 4, 8, 16
2X TID	0, 0.25, 16	Trough	Trough	Trough	Trough	0, 8, 16
3X BID	0, 0.25, 12	Trough	Trough	Trough	Trough	0, 12

A pharmacokinetic analysis of the 1X groups was performed, but due to the limitations in the timing of blood sample collections, an analysis of the 2X TID and 3X BID groups was not conducted. The observed maximum concentration (C_{max}) was used in the pharmacokinetic analysis of the 1X groups instead of initial concentration (C_0) because the limited number of samples increased the potential for error in extrapolating to C_0.

Table III.10a: Comparison of pharmacokinetic parameters following administration of a single IV dose of 30mg/kg Zimeta™ on Days 1 and 9; (horses were dosed twice daily for 9 days)

Variable	Units	Group	Day 1-Mean	Day 1-SD	Day 9-Mean	Day 9-SD
Cmax	ng/mL	1XBID	40616.67	9917.34	48500.00	15858.25
Cmin	ng/mL	1XBID	2466.68	592.71	3705.00	1899.57
Cavg	ng/mL	1XBID	8904.06	1010.74	11354.24	2832.064
AUCtau	hr*ng/mL	1XBID	106848.75	12128.88	136250.80	33984.77
HL_Lambda_z	hour	1XBID	3.94	0.44	4.52	1.34
CLss	mL/kg/hr	1XBID	284.17	36.08	229.96	67.40
Vz	mL/kg	1XBID	1607.43	165.51	1447.21	226.46

AUCtau= area under the curve for the dosing interval (12 hours)
CLss= clearance at steady state
Cmax= maximum concentration
Cavg= average plasma concentration over the dosing interval
Cmin= minimum concentration
HL_Lambda_z= half-life estimated using terminal phase (lambda z); 1-12 hours
Vz= volume of distribution estimated using lambda z

Table III.10b: Comparison of pharmacokinetic parameters following administration of a single IV dose of 30mg/kg Zimeta™ on Days 1 and 9; (horses were dosed three times daily for 9 days)

Variable	Units	Group	Day 1-Mean	Day 1-SD	Day 9-Mean	Day 9-SD
Cmax	ng/mL	1XTID	57775.00	6479.39	65625.00	7841.08
Cmin	ng/mL	1XTID	4671.11	2084.37	9455.88	5113.72
Cavg	ng/mL	1XTID	15521.81	1887.21	22221.64	3515.83
AUCtau	hr*ng/mL	1XTID	124174.38	15097.72	177773.13	28126.64
HL_Lambda_z	hour	1XTID	3.57	0.35	5.76	0.71
CLss	mL/kg/hr	1XTID	244.47	31.60	172.21	29.30
Vz	mL/kg	1XTID	1253.12	117.98	1413.96	122.89

AUCtau= area under the curve for the dosing interval (8 hours)
CLss= clearance at steady state
Cmax= maximum concentration
Cavg= average plasma concentration over the dosing interval
Cmin= minimum concentration
HL_Lambda_z= half-life estimated using terminal phase (lambda z); 1-8 hours
Vz= volume of distribution estimated using lambda z

Conclusions: The absence of coagulopathy in any treatment group, and specifically the 2X and 3X BID groups, supports the conclusion that there is an adequate margin of safety when dipyrone injection is administered at 30 mg/kg IV up to twice daily (every 12 hours). However, the data did demonstrate numerical trends towards increasing prothrombin time with increased dipyrone dosing frequency, suggesting a treatment effect. Finally, this study supported the conclusion that the respiratory disease, and the severity of clinical signs of respiratory disease, observed in study KB0122 was not likely related to the administration of dipyrone injection.

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: For intravenous use in horses only. Do not use in horses intended for human consumption. Do not use in any food producing animals, including lactating dairy animals.

V. USER SAFETY

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

Human Warnings: Care should be taken to ensure that dipyrone is not accidentally injected into humans as studies have indicated that dipyrone can cause agranulocytosis in humans. Not for use in humans. Keep out of reach of children. Consult a physician in case of accidental human exposure. Direct contact with the skin should be avoided. If contact occurs, the skin should be washed immediately with soap and water. As with all injectable drugs causing profound physiological effects,

routine precautions should be employed by practitioners when handling loaded syringes to prevent accidental self-injection.

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 Zimeta™, when used according to the label, is safe and effective for the control of pyrexia 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 required to administer the product intravenously.

B. Exclusivity

Zimeta™, 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 (FD&C Act) because this is the first time we are approving this active ingredient 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 Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.