Date of Approval: February 13, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-420

TILDREN

tiludronate disodium

Powder for injection

Horse

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

Sponsored by:

Ceva Sante Animale

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I. GENERAL INFORMATION

A. File Number

NADA 141-420

B. Sponsor

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France

Drug Labeler Code: 013744

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C. Proprietary Name

TILDREN

D. Established Name

Tiludronate disodium

E. Pharmacological Category

Bisphosphonate

F. Dosage Form

Powder for injection

G. Amount of Active Ingredient

500 mg tiludronate disodium

H. How Supplied

1 vial containing 500 mg tiludronate disodium lyophilized powder

I. Dispensing Status

Rx

J. Dosage Regimen

A single dose of 1 mg tiludronate disodium/kg body weight (0.45 mg/lb) administered as an intravenous infusion slowly and evenly over 90 minutes to minimize the risk of adverse reactions

K. Route of Administration

Intravenous infusion

L. Species/Class

Adult horses, 4 years and older

M. Indication

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

II. EFFECTIVENESS

A. Dosage Characterization

The justification for selection of a dose of 1 mg/kg tiludronate administered as a single intravenous (IV) infusion in the horse is based on extrapolation from a dose having produced at least 75% inhibition in a model of bone resorption in the rat. The 1 mg/kg dose produces bone concentrations in the horse within the range of concentrations known to inhibit bone resorption *in vivo* in mice. A clinical trial compared the efficacy of tiludronate at 0.5 mg/kg and 1 mg/kg administered in daily IV doses of 0.1 mg/kg for 5 or 10 consecutive days, respectively, for the treatment of navicular disease in horses[1]. The study reported improvement of clinical signs and level of exercise with tiludronate administered intravenously at a total dose of 1 mg/kg. Pharmacokinetic justification for selection of 1 mg/kg tiludronate administered once as an intravenous infusion to be further evaluated in field studies is based on the comparative bioavailability study (Study MPK/145R1/0504) which compared the same total dose of 1 mg/kg delivered as a 30-minute infusion to 10 daily doses of 0.1 mg/kg. The study was conducted in 12 healthy Standardbred horses (6 geldings + 6 non-pregnant females) that were randomized to the two treatment groups. The pharmacokinetic parameters of clearance (Cl) and area-under-the-curve (AUC) of tiludronate administered by either regimen were not statistically different, and the relative plasma bioavailability of the single 1 mg/kg infusion versus the 10-day infusion of 0.1 mg/kg was 103%.

B. Substantial Evidence

1. Field Effectiveness Study

a. Title: The Clinical Effectiveness of Code 145R1 (tiludronate disodium) in equine navicular syndrome characterized by predominantly bony lesions (Study # ST-CLI/145R1/0611). July 2007-January 2009

[1] Denoix JM, Thibaud D, Riccio B. Tiludronate as a new therapeutic agent in the treatment of navicular disease: a double-blind placebo-controlled clinical trial. *Equine Vet J*. 2003; 35(4): 407-13.

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c. Study Design:

(1) Objectives:

(a) To evaluate the effectiveness of tiludronate disodium plus corrective shoeing in improving lameness and other clinical signs associated with equine navicular syndrome when the primary pathology involves the navicular bone itself with minor soft tissue involvement.

(b) To compare the effectiveness of tiludronate disodium plus corrective shoeing with the effectiveness of corrective shoeing alone.

(2) Study Animals: 208 adult (4-20 years old) horses diagnosed with navicular syndrome were enrolled in the study. 204 cases completed the study (136 tiludronate-treated and 68 vehicle-treated). The 208 horses in the study included 46 mares, 156 geldings, and 6 stallions that weighed between 821 and 1530 pounds. Breeds enrolled included 128 American Quarter Horses or Quarter Horse crosses (62%), 24 Thoroughbreds or Thoroughbred crosses (12%), 23 Paints (11%), 19 various Warmblood breeds (9%), 6 Appaloosas (3%), 3 Arabian or Arabian crosses (1%), and 1 each of Welsh cross pony, Pinto, Mustang, Foxtrotter, and Grade (<1%).

Bilateral lameness comprised 78% of the cases. Duration of lameness attributable to navicular disease was variable; however, the majority of horses enrolled had a history of navicular disease of less than 6 months duration.

(3) Dosage and Administration: Horses were randomly assigned to one of two treatment groups (See Table 1).

Table 1. Treatment Groups

Tx Group	Treatment	Number of Animals Enrolled (Evaluable)
TILDREN	1 mg/kg tiludronate disodium	139 (119)
Vehicle Control	250 mg mannitol (excipient)	69 (62)

Treatment consisted of a single intravenous infusion of either TILDREN (tiludronate disodium, final market formulation) diluted in 1 L of 0.9% sterile saline or control (excipient) diluted in 1 L of 0.9% sterile saline. All horses received corrective shoeing. Investigators were masked to treatment group.

Each vial of test article was reconstituted with 25 mL of 0.9% sterile saline prior to dilution in the 1 L saline infusion bag. The volume of test article to be introduced into the 1 L saline bag was determined based on the following chart for each horse:

Table 2. Dosing Chart

Weight Range (lbs)	Volume of Test Article to be Added to 1 L Saline (mL)
551-771	15
772-991	20
992-1211	25
1212-1432	30
1433-1652	35
1653-1874	40

(4) Route of Administration: TILDREN (tiludronate disodium) was reconstituted in 1 L 0.9% saline, and administered as an intravenous administration over 30 minutes. Due to incidence of adverse events at the 30 minute infusion time, a protocol amendment extended the infusion time to 60 minutes during the study.

(5) Study Duration: Final evaluation for each horse was performed 2 months ±4 days following administration of the test article. Following completion of the controlled study, horses were selected to participate in an open field safety study (Study 0705, Field Safety Study).

(6) Inclusion criteria:

(a) Horses 4 years of age and older

(b) Diagnosis of navicular syndrome based on all of the following: lameness examination, absence of other causes of palmar foot pain, lameness alleviated by palmar digital nerve block, and bone edema in the navicular bone medullary cavity on MRI with no major soft tissue involvement.

(c) Lameness Grade of 2 or 3 (on a 0-5 scale) in the lamest limb when trotting in a 10-meter circle on a firm, level surface with the lamest limb on the inside.

(d) Absence of abnormal serum BUN, creatinine, or calcium values

(e) Absence of renal disease or disease affecting calcium homeostasis

(7) Measurements and Observations: Horses were initially evaluated by general physical examination, clinical pathology, and lameness examination (conformation, limb palpation, hoof tester examination, flexion tests, assignment of lameness score, and palmar digital nerve block [PDNB]) at the initial evaluation prior to treatment. Radiographs and MRI evaluation of both front feet were performed in this initial evaluation. Post-treatment follow-up visits were scheduled at 2 weeks (± 1 day), 1 month (± 3 days), and 2 months (± 4 days) post-treatment. Physical and lameness examinations were repeated at 2 weeks, 1 month, and 2 months. Clinical pathology evaluations were repeated at 2 weeks and 1 month.

Lameness was evaluated on a firm level surface at a walk, straight line trot, and trotting in a 10-meter circle to the left and right. A lameness score was assigned as follows:

0 No detectable lameness
1 Difficult to observe except under special circumstances such as circling; not lame at a walk or straight line trot.
2 Difficult to observe at a walk; mild inconsistent lameness at a straight line trot; obvious consistent lameness with head nod on circle.
3 Consistent lameness with a head nod at a straight line trot; marked head nod on a circle.
4 Severe lameness with a marked head nod at a straight line trot; lameness obvious at a walk.
5 Minimal weight-bearing in motion and/or at rest; non-weight-bearing.

Horses were closely monitored for adverse reactions for four hours post-treatment. Injection sites were examined at the end of this period.

d. Statistical Methods: The primary effectiveness variable was a successful outcome, defined as an improvement by 1 lameness grade or more, compared to baseline, at the 2-month follow-up assessment, in the lamest

limb when trotting in a 10-meter circle with the lamest limb on the inside of the circle, and no worsening of lameness in the opposite limb. The statistical analysis compared the treatment groups using a generalized linear mixed effect model (GLIMMIX procedure in SAS) in which Treatment served as a fixed effect and Site and Treatment x Site interactions were random effects.

e. Results:

Of 835 screened horses, 208 (25%) met all the inclusion criteria and were enrolled in the study. 28 horses were excluded from the effectiveness database. The most common reasons for exclusion included: data integrity concerns in individual cases, injury, withdrawal for reasons unrelated to the study, and enrollment of horses that did not fit the inclusion criteria.

The effectiveness analysis was based on 181 horses. The success rate 2 months post-treatment is shown in Table 3.

Table 3. Success at 2 Months Post-Treatment

Group	Number of Subjects	Success Rate (%)	P-Value
Placebo	62	48.39	----
TILDREN	119	63.87	0.0479

f. Adverse Reactions:

In the controlled field study, horses were observed closely for 4 hours following the infusion. Clinical signs associated with colic were observed during the infusion or during the post-infusion observation period in 57 of 139 (41%) of tiludronate treated horses and 7 of 69 (10%) placebo treated horses. Clinical signs that were considered to be indicative of colic included pawing, evidence of pawing, getting up and down, pacing, restlessness, rolling, trying to roll, looking or biting at side, stretching out/straining, kicking at belly/walls, and repeatedly shifting weight behind.

Due to the incidence of adverse reactions with the 30 minute infusion, a protocol amendment was issued during the field study directing the investigators to give the infusion over 60 minutes instead of 30 minutes. Thirty-five of 60 (58%) horses administered TILDREN over approximately 30 minutes had colic signs. Twenty-two of 79 (28%) horses administered TILDREN over approximately 60 minutes had colic signs. Both Chi-square ($p<0.0001$) and Fisher's Exact ($p<0.0001$) tests indicate that there is a significant association between 30 min and 60 min infusion times and incidence of colic.

Severity and duration of colic signs varied. Treatment of colic with drugs was instituted in 24 horses out of 139 TILDREN treated (16.5%) animals in the controlled study. There was no difference in the duration of colic signs when comparing the 30- and 60-minute infusion groups.

Of the 57 TILDREN treated horses exhibiting signs of abdominal discomfort, 33 (58%) were not treated with drugs to address these signs.

In horses not treated with drugs for colic signs, the duration of signs varied between 7 minutes to 6 hours 35 minutes (mean 81 min). Twenty-four horses were treated with drugs for post-TILDREN infusion abdominal discomfort; 22 horses received one dose of flunixin, either alone (18) or flunixin combined with other treatments (4). Other medications used included detomidine, xylazine, butorphanol, and n-butylscopolammonium bromide. Signs of colic in these horses resolved within 10-15 minutes following treatment.

Adverse reactions are listed in Table 4 below:

Table 4: Adverse Reactions in the Field Effectiveness Study

Adverse Reaction	Number of TILDREN Treated Horses Exhibiting Adverse Reaction (%) in Controlled Study	Number of Placebo Treated Horses Exhibiting Adverse Reaction (%) in Controlled Study
Colic-Post-Infusion[1]-within 24 hours post-infusion	57 (41%)	7 (10%)
Injection site swelling/hematoma	12 (9%)	5 (7%)
Frequent urination[2]-within 4 hours of infusion	6 (4%)	1 (1%)
Muscle fasciculations-within 4 hours of infusion	4 (3%)	0 (0%)
Polyuria ± polydipsia (longer than 4 hours post-infusion)	7 (5%)	0 (0%)
Inappetence/anorexia	7 (5%)	0 (0%)
Sore neck/stiffness	2 (1%)	0 (0%)
Fever	2 (1%)	0 (0%)
Colic (not immediately post-infusion)	2 (1%)	0 (0%)
Large Colon Impaction	1 (<1%)	0 (0%)

[1]defined as having at least one of the following signs: pawing, evidence of pawing, getting up and down, pacing, restlessness, rolling, trying to roll, looking or biting at side, stretching out/straining, kicking at belly/walls, and repeatedly shifting weight behind
[2]defined as greater than two episodes in the four hour observation period or two episodes in less than one hour

Clinical pathology (complete blood count and serum chemistry) was evaluated pre- and/or post-treatment with flunixin in 19 horses. The administration of flunixin was associated with a statistically significant ($p=0.0006$) rise in creatinine levels. Elevations in creatinine above the reference range following flunixin treatment ranged from 1.8-2.7 mg/dL. Six of the 19 (32%) horses with clinical pathology data had creatinine values above the reference range following treatment with flunixin. These elevations of creatinine did not persist 2 weeks later. BUN, calcium, and magnesium were also elevated when compared to baseline values following treatment with flunixin.

Three TILDREN treated horses (2%) that did not colic had elevated creatinine values at one or more of the follow up visits. These horses did not demonstrate adverse clinical signs associated with the elevation in creatinine. No placebo horses with normal creatinine values at baseline had elevated creatinine values at subsequent time points.

g. Conclusions: TILDREN administered at approximately 1 mg/kg by intravenous infusion over 30 or 60 minutes, in addition to corrective shoeing, is effective in controlling clinical signs associated with navicular syndrome. However, this dosing regimen may be associated with a high incidence of colic signs. Treatment of colic signs with NSAIDs may adversely affect renal function. Long term effects on renal function are unknown.

2. Pharmacokinetic Modeling Studies

The sponsor conducted an additional safety study (Study US/CLI/145R1/1201) to monitor for adverse events following a 90 or 120 minute infusion, and used a pharmacokinetic (PK) simulation to bridge the 30 and 60 minute infusion effectiveness data to the 90 and 120 minute infusion field safety data. The dose linearity of tiludronate disodium had been demonstrated in two PK studies in six horses (ST-MPK/145R1/0504 and ST-MPK/145R1/0512), in which the 1 mg/kg dose was delivered in a 30 minute infusion. The data from these two studies were used to simulate the PK parameters of the same dose delivered in 60, 90, and 120 minute infusions. Table 5 compares the mean observed and predicted concentrations at 30, 60, 90 minutes, and at 12, 24, and 48 hours post-infusion. The longer infusion times resulted in a lower maximum concentration (Cmax). The mean Cmax for the 30, 60, 90, and 120 minute infusions were 8.23, 7.07, 6.22, and 5.57 mcg/mL respectively. The mean area-under-the-curve to the limit of quantification (AUC_{LOQ}) and clearance (CL) were 34.35 hr*mcg/mL and 30.98 mL/hr/kg respectively for all infusion times.

Table 5: Mean Observed and Simulated Tiludronate Plasma Concentrations (mcg/mL) Following Different Rates of Infusion

Time After Start of Infusion	Mean Plasma Concentration (mcg/mL) 30 Min Infusion (Observed)	Mean Plasma Concentration (mcg/mL) 30 Min Infusion (Simulated)	Mean Plasma Concentration (mcg/mL) 60 Min Infusion	Mean Plasma Concentration (mcg/mL) 90 Min Infusion	Mean Plasma Concentration (mcg/mL) 120 Min Infusion
30 min	7.72	7.65	3.41	2.27	1.71
60 min	5.90	5.90	7.06	4.72	4.46
90 min	4.31	4.31	4.94	5.84	4.86
120 min	3.61	3.61	4.07	4.68	5.56
12 hours	0.50	0.50	0.51	0.53	0.55
24 hours	0.18	0.18	0.18	0.18	0.19
48 hours	0.08	0.08	0.08	0.08	0.08

Based on simulations, the concentration at 12, 24, and 48 hours is not compromised by changes in infusion rate. This is not unexpected, as the

terminal elimination half-life of this drug is longer than the proposed maximum duration of drug infusion. Moreover, with the assumption of linear pharmacokinetics based upon prior data generated for this drug, there should be no change in clearance with change in peak concentrations and therefore no change in total drug exposure (AUC). In published studies on bisphosphonate activity in human patients, it was observed that the AUC is the parameter most closely correlated to therapeutic outcome. Therefore, based upon the simulated results of an infusion conducted over 60, 90, or 120 minutes, the infusion time of 90 minutes will not negatively impact product effectiveness.

III. TARGET ANIMAL SAFETY:

A. Laboratory Safety

1. U.S. Target Animal Safety Study

a. Title: Study ST-MPK/145R1/0419: Pivotal target species safety study of Code 145R1 (tiludronic acid) in the horse. July 2005-March 2006

b. Study Location:

Sallisaw Equine Clinic
Sallisaw, OK

c. Study Design:

(1) Objective: To determine the systemic safety of Code 145R1 in the target species when administered at 1, 3, and 5 times the recommended dose.

(2) Study Animals: 30 horses, females and geldings, aged 3-5 years old

(3) Experimental Design: Horses were divided into 4 dose groups and 1 control group, each consisting of 6 horses. Horses were randomly assigned to one of the 5 treatment groups in 2 replicates.

(4) Drug Administration: The test article was the final market formulation of TILDREN, tiludronate disodium, 500 mg powder for reconstitution with 0.9% sodium chloride solution. The control was 20% mannitol (vehicle) diluted with a similar volume of 0.9% sodium chloride solution as the 5X group. There were five treatment groups. One 1X (1 mg/kg) treatment group received one treatment of TILDREN only. The remaining four treatment groups, 1X (1mg/kg), 3X (3 mg/kg), 5X (5 mg/kg), and vehicle control (0 mg/kg) received three treatments at one month intervals. The infusion for the 1X group was administered at 4 mg/kg/hr. The dose for the 3X and 5X groups was diluted in a proportionate volume of 0.9% sodium chloride and the infusion rate was approximately 2 mg/kg/hr. In this study, TILDREN was administered while horses stood in stocks and with an infusion pump for steady delivery. See Table 6.

Table 6: Treatment Groups

Group	Tx	No. and Sex of Horses	Dose	Infusion Volume	Rate of Infusion	Duration of Infusion	Total No. of Doses
1	TILDREN	6 (3M, 3F)	1mg/kg (1x)	1 L	4 mg/kg/hr	15 min	1
2	TILDREN	6 (3M, 3F)	1mg/kg (1x)	1 L	4 mg/kg/hr	15 min	3*
3	TILDREN	6 (3M, 3F)	3mg/kg (3x)	3 L	2mg/kg/hr	90 min	3*
4	TILDREN	6 (2M, 4F)	5mg/kg (5x)	5 L	2mg/kg/hr	150 min	3*
5	Vehicle control	6 (4M, 2F)	Vehicle	5 L	n/a	150 min	3*

* Doses were given once/month for three consecutive months

(5) Measurements and Observations: Physical examination, endoscopic examination of the stomach (prior to baseline period), body weight, daily health checks, immediate post-treatment observations, hematology, serum chemistry (including ionized calcium), urinalysis, pulse rate, respiratory rate, blood pressure, gross pathology and histopathology.

(6) Bone Studies: 17 days prior to euthanasia, all horses were administered intravenous oxytetracycline 25 mg/kg body weight diluted in 500 mL saline. 7 days prior to euthanasia, all horses were administered intravenous calcein green 15 mg/kg body weight diluted in sodium bicarbonate. Following euthanasia, bones (3rd metatarsal/metacarpal, 3rd carpal, and forelimb navicular) were harvested and processed for evaluation of mechanical properties (structural and material strength), bone density, histology and histomorphometry.

d. Statistical Methods: For the continuous variables measured at more than one time point a repeated measures analysis of covariance model was performed to test the effects of dose group, time, sex, and all the two and three-way interactions. Baseline measurements were included in the model as covariates. For continuous variables measured once an analysis of variance model was performed to test the effects of dose group, sex and the two-way interaction. Follow-up pairwise least square mean comparisons between the control group and each treatment group, between baseline and post-baseline, and between different time points with each group were performed, using linear contrasts with significance level 0.10.

e. Results:

(1) General health observations (excluding immediate post-treatment colic): One horse had mild transient injection site swelling following treatment (Group 2-1X, three doses). Two horses developed colic signs outside of the 4 hr post-treatment window. One horse with colic (Group 5-control) was diagnosed with a large colon impaction. The other horse with colic (Group 2-1X, three doses) developed severe signs of colic and was treated for proximal enteritis one day following the third treatment with TILDREN.

(2) Post-treatment observations:

(a) Colic: Clinical signs consistent with colic were noted during the infusion and in the immediate post-treatment period. Attributing these clinical signs to treatment-related colic during infusion was complicated due to the fact that the infusion was administered in stocks and horses in the 3X, 5X, and control groups were confined to stocks for approximately 1½ hr (3X) and 2½ hr (5X). Naturally, more horses in these groups developed signs of restlessness toward the end of these infusions. However, other clinical signs of colic, including pawing, getting up and down, sweating, and looking at flanks were observed following completion of the infusion once horses were back in their stalls. See Table 7 for details.

Table 7: Number of Observations of Abnormal Clinical Signs During or Following the Infusion

Group (Treatment)	Signs of Restlessness or Agitation Occurring During the Infusion/Number of Infusions	Clinical Signs of Colic Following Infusion/Number of Infusions
Group 1 (1 mg/kg, 1 dose)	0/6 (0%)	1/6 (16%)
Group 2 (1 mg/kg, 3 doses)	0/18 (0%)	2/18 (11%)
Group 3 (3 mg/kg, 3 doses)	7/18 (38%)	5/18 (28%)
Group 4 (5 mg/kg, 3 doses)	7/18 (38%)	6/18 (33%)
Group 5 (control, same duration as Group 5)	10/18 (55%)	1/18 (6%)

(3) Clinical pathology:

(a) Calcium: Serum ionized calcium (ICa) was measured for short-term changes at 2, 4, 6, 24 and 48 hours following TILDREN infusion. There were significant ($p<0.10$) differences in short-term group means for ICa on multiple occasions during the 1st and 2nd treatment cycles. The group 4 (5X) mean was significantly lower than the group 5 (control) mean at the end of the 1st infusion, and 4, 6, and 72 hours post-infusion. Also, the group 4 means were significantly lower during the 2nd treatment cycle at the end of infusion, and 4 and 72 hours post-infusion. All TILDREN group means were significantly lower than control 6 hours post-infusion during the 1st treatment cycle. Group 3 (3X) also had a significantly lower mean value than group 5 (control) 72 hours post-infusion during the 1st treatment. ICa was measured for long-term changes on study days 35, 65, 95 and 125. Long-term individual values for ionized calcium were all within the reference range, except for one very mild decrease.

(b) Phosphorus: A statistically significant effect on serum phosphorus was seen at 72 hours post-treatment, in which groups 3 (3X) and 4 (5X) had higher mean serum inorganic phosphate levels than either group 5 (control) or the two lower dose treatment groups. Values in group 4 (5X) exceeded the upper limit of the reference range at 72 hours. This increase in phosphorus was not consistently correlated with decreased ICa in individual horses.

(c) Renal parameters: BUN and creatinine were measured at the same time points as ICa. For BUN, group mean values were within the reference range. Only one horse showed a substantial elevation in BUN. This horse in group 3 (3X) had a value of 40 mg/dL correlating with an episode of colic. For creatinine, multiple values were above the reference range at varying time points, including at baseline and in the control group. More horses in the treated groups had increases in serum creatinine following treatment than the control group (Table 8). Two horses in the control group had consistently elevated creatinine values throughout the study, including at baseline measurements. Outside of these two horses, elevations in individual creatinine values ranged from 1.7-2.3 mg/dL (reference range 0.8-1.6 mg/dL).

Table 8: Horses with Creatinine Values Above the Reference Range* (6 Horses Per Treatment Group)

Group # (Treatment)	# of Horses Elevated at Baseline	# of Horses Elevated After Treatment 1	# of Horses Elevated After Treatment 2	# of Horses Elevated After Treatment 3
Group 1 (1X, 1 dose)	3	4	NA	NA
Group 2 (1X, 3 doses)	2	2	3	4
Group 3 (3X, 3 doses)	1	3	2	3
Group 4 (5X, 3 doses)	1	3	3	4
Group 5 (vehicle, 3 doses)	3	3	3	2

*Using the reference range from the testing laboratory: 0.8-1.6 mg/dL. A horse was counted as having elevated creatinine if it had a value above 1.6 at any time point following treatment, but prior to the subsequent treatment.

(d) Liver enzymes: There was a statistically significant increase in group mean Gamma Glutamyl Transferase (GGT) and Sorbitol Dehydrogenase (SDH) values for Group 3 (3X) on Day 35 when compared to Group 5 (control). One Group 3 horse had elevated GGT and SDH values on Day 35 and 72 hours following treatment 2. In this same horse, GGT was also elevated on Day 65 and 72 hours following treatment 3.

(4) Pathology: Gross lesions were noted in the kidneys of some horses from all treatment groups, including pale, focal depressed areas in the cortex and rough and irregular kidney surfaces.

(5) Histopathology: Histopathology lesions were found in the kidneys of horses in all treatment groups (including control groups). Lesions were described as mild to moderate tubular necrosis of the proximal and distal convoluted tubules, with cell sloughing and regeneration, and with occasional involvement of Henle's loop, and rarely tubular dilatation and peritubular fibrosis.

(6) Bone studies: No abnormal bone tissue was formed in the examined specimens. No abnormal bone resorption sites were seen. Numbers and locations of cortical and cancellous bone remodeling units reflected normal processes.

f. Conclusions: A dose-dependent increase in clinical signs of colic was seen following TILDREN infusion at the rate of 2-4 mg/kg/hr. Renal safety could not be determined, due to potentially confounding co-administration of oxytetracycline to all animals for bone studies.

2. Renal Safety Study

a. Title: Study US/TAS/145R1/1001: Target Animal Safety Study of Code 145R1 (tiludronate disodium) to Assess the Renal Safety in the Horse. June 2010-August 2010

b. Study Location:

East Tennessee Clinical Research
Rockwood, TN

c. Study Design:

(1) Objective: The objective of the study was to assess the renal safety of tiludronate disodium in the horse when administered at the recommended dose (1X) and at three times the recommended dose (3X) repeated 3 times at 10-day intervals.

(2) Study Animals: 12 healthy horses (males and females) aged 3-5 years

(3) Experimental Design: Horses were randomized into 3 groups of 4 horses. Within gender, horses were randomized to treatment groups (2 males and 2 females per group) on study Day 3 without regard for body weight. Three treatments were administered by intravenous infusion, each 10 days apart. Treatments were administered on Day 9, Day 19, and Day 29 of the study. Horses were euthanized and necropsied on Day 33.

(4) Drug Administration: The test article was the final market formulation of TILDREN, tiludronate disodium, 500 mg powder for reconstitution with 0.9% sodium chloride solution. Group 1 horses (negative control) were administered 500 mL infusion of 0.9% sodium chloride solution. Group 2 horses (1X) were administered TILDREN infusion at 1 mg/kg diluted in 500 mL of 0.9% sodium chloride. Group 3 horses (3X) were administered TILDREN infusion at 3 mg/kg diluted in 1 L of 0.9% sodium chloride. Three treatments were administered by intravenous infusion, each 10 days apart. The infusion rate was delivered by infusion pump at 4 mg/kg/hr to horses treated with the test article. See Table 9.

Table 9: Treatment Groups

Treatment Group	Number of Horses	Dosage (mg/kg BW)	Volume of Infusion	Rate of Infusion	Duration of Infusion	Number of Doses
1	4	0X (0 mg/kg)	500 mL	NA	15 min.	3
2	4	1X (1 mg/kg)	500 mL	4 mg/kg/hr	15 min.	3
3	4	3X (3mg/kg)	1 L	4 mg/kg/hr	45 min.	3

(5) Measurements and Observations: Physical examination, post-treatment clinical observations, hematology, serum chemistry, urinalysis, renal ultrasound, renal biopsy, renal gross and histopathology.

d. Statistical Methods: For continuous outcomes measured once (such as clinical pathology results, body weight, kidney weight as a percentage of final body weight), ANCOVA or ANOVA (as appropriate, the MIXED

procedure in SAS, SAS Institute, Gary, North Carolina) was used to evaluate a model containing treatment, gender, and gender-by-treatment interaction as fixed effects. For continuous outcomes measured repeatedly (such as water consumption), repeated measured ANCOVA was used. Treatment, gender, day, and all the two-way and three-way interactions were included in the model as fixed effects. If baseline values existed, the values closest to the treatment were used as a covariate. Regardless of the statistical significance of the covariate, it was retained in the statistical model. The Kenward-Roger's adjustment was used to adjust the degrees of freedom. Categorical variables were summarized by counts and percentages; no hypothesis testing was conducted with these outcomes.

e. Results:

(1) Post-treatment observations: Two Group 2 horses (1X) and one Group 3 horse (3X) demonstrated clinical signs of colic following the first TILDREN infusion. Colic signs resolved without treatment. No other treatment related adverse events were recorded.

(2) Clinical pathology: No clinically significant changes in hematology or serum chemistry were noted, including BUN and creatinine.

(3) Renal gross pathology: A few gross lesions occurred in the control and 1X groups. These were considered to be naturally occurring (not related to treatment) or iatrogenic from renal biopsy procedures. No gross lesions were seen in the 3X groups.

(4) Renal histopathology: A variety of histopathologic lesions were observed in the kidneys from all groups, including the control group. Lesions that could be considered potentially treatment related included tubular necrosis and interstitial lymphocytic nephritis. Most of these lesions were considered mild by the study pathologist. Lesions observed could be also be consistent with exposure to parasites (e.g. *Klossiella equi*), and bacteria (e.g. *Streptococcus* spp.) There was no clear evidence of renal toxicity induced by TILDREN.

f. Conclusions: Administration of TILDREN at 1 mg/kg (1X) and 3 mg/kg (3X) at an infusion rate of 4 mg/kg/hr in horses with normal renal function did not demonstrate evidence of renal toxicity.

3. Hyperkalemic Periodic Paralysis Safety Study

a. Title: Safety of Code 145R1 when Administered to Horses Carrying the Gene for Hyperkalemic Periodic Paralysis (HYPP). Study number US/CLI/145R1/1202. July-September 2012

b. Study Location:

East Tennessee Clinical Research
Rockwood, TN

c. Study Design:

(1) Objective: To assess the safety of TILDREN when administered at the recommended dose of 1 mg/kg to horses carrying the gene for HYPP. This study was performed due to the death of one horse that was heterozygous for HYPP in the field safety study (0705).

(2) Study Animals: 12 American Quarter Horses, heterozygous for the HYPP gene

(3) Experimental Design: Twelve horses (6 per treatment group) were randomized to receive either TILDREN (tiludronate disodium), or 0.9% saline (negative control). Each horse received two treatments, approximately 30 days apart, with no crossover.

(4) Drug Administration: TILDREN (final market formulation) reconstituted in 1 L of 0.9% saline or 1 L 0.9% saline (control) was administered as an intravenous infusion over 90 minutes.

(5) Measurements and Observations: Physical examination, hematology, serum chemistry, and serum electrolytes were performed prior to infusion. Horses were continuously observed 30 minutes prior to infusion, during the infusion, and for 4 hours following the end of the infusion. If abnormal signs were noted, clinical examinations were performed and serum potassium was evaluated every 30 minutes until the values were normal or until clinical signs resolved.

d. Statistical Methods: The primary safety criterion was the incidence of clinical signs associated with HYPP in the control versus treated group. In addition, HYPP severity score between groups was assessed. The incidence of HYPP was summarized by percent HYPP episodes and 95% confidence intervals using the Clopper-Pearson method. Results collected after each dose and the cumulative incidence across the two doses were summarized in this manner. Additionally, the incidence of colic after each dose was analyzed using Fisher's Exact Test (the Freq Procedure in SAS) to test the difference between groups. A significant level of 0.1 was used. Results from each dose were analyzed separately. Severity of HYPP in each group was summarized by frequencies within a severity ranking. No hypothesis testing was conducted.

e. Results:

(1) HYPP: See Table 10 for a summary of clinical signs of hyperkalemia associated with infusion. One TILDREN horse had signs consistent with colic following the first infusion (laying down, looking at sides, rolling, and pawing). The results from the blood sample corresponding to the clinical signs were inconclusive, as sampling was performed with the wrong collection tube. This horse also had muscle fasciculations of the trapezius muscle. The horse was not treated for colic or HYPP, and recovered without incident.

One horse assigned to the control group inadvertently was administered TILDREN during the second infusion. This horse had

clinical signs about 10 minutes into the second infusion that could be consistent with a hyperkalemic episode (grunting, muscles tightening up); however, serum potassium remained normal during the episode.

One control horse exhibited muscle fasciculations after the first infusion, with increasing serial serum potassium levels; however, all serum potassium values were within normal limits. Two horses in the control group exhibited clinical signs consistent with HYPP (with elevated serum potassium levels) between treatments that resolved with hand walking, with or without administration of oral corn syrup. These episodes were accompanied by significant elevations in serum potassium.

Table 10. Clinical Signs of Hyperkalemia During or in the 4 Hours Following TILDREN Infusion in Horses Heterozygous for HYPP

Treatment Group	Number of Horses with Possible Clinical Signs* of Hyperkalemia Infusion 1	Number of Horses with Confirmed Hyperkalemia Infusion 1	Number of Horses with Possible Clinical Signs* of Hyperkalemia Infusion 2	Number of Horses with Confirmed Hyperkalemia Infusion 2
TILDREN	1	0	1	0
Saline control	1	0	0	0

*muscle fasciculations have been noted to occur in normal horses (negative for HYPP gene) following the administration of TILDREN

(2) Colic: Treated horses demonstrated signs of colic either during or in the 4 hours following TILDREN infusion. See Table 11. All signs resolved without medical treatment, although some horses were hand-walked in order to resolve clinical signs. One horse showed signs of colic immediately before the second treatment, and this horse's treatment day was delayed (still within the study period). The colic signs resolved, and the horse did not exhibit further signs of colic during or after the second infusion of TILDREN.

Table 11. Clinical Signs of Colic in Horses Heterozygous for HYPP

Treatment Group	Number of Horses with Colic (%) (Infusion 1)	Number of Horses with Colic (%) (Infusion 2)
TILDREN	1 (16.7%)*	5 (71%)
Saline control	0 (0%)	0 (0%)

*Two additional TILDREN horses were noted to paw, but for very brief periods and not accompanied by any other signs of colic

f. Conclusions: Administration of TILDREN at a dose of 1 mg/kg (1X) by intravenous infusion over 90 minutes did not induce hyperkalemic episodes in horses heterozygous for the HYPP gene (H/N). A second dose of TILDREN may increase the risk or severity of colic signs in horses with the gene for HYPP. The effect of TILDREN administration on horses homozygous for the HYPP gene (H/H) is unknown.

B. Field Safety:

1. Field Safety Study:

a. Title: Extended use safety study of Code 145R1 (tiludronate disodium) in equine navicular syndrome under typical field conditions. Study number: ST-CLI/145R1/0705. October 2007-June 2009

b. Investigators: Same as field effectiveness study (ST-CLI/145R1/0611)

c. Study Design:

(1) Objective: To provide extended field safety information under conditions of use, including the use of concomitant medications.

(2) Study Animals: All placebo (negative control) horses and randomly selected TILDREN treated horses from the effectiveness field trial (Study #ST-CLI/145R1/0611) were eligible to enroll in the field safety study.

(3) Experimental Design: For 6 months, horses were evaluated at monthly intervals and could receive a TILDREN infusion at any of the monthly visits. There were no restrictions on the number of doses of TILDREN that a horse could receive except that treatment was discontinued if BUN, creatinine, or calcium values were found to be outside the reference range at the monthly visits. Concurrent medications were allowed during the 6 month study with observed wash out periods prior to the monthly visits.

(4) Drug Administration: TILDREN (tiludronate disodium) was reconstituted in 1 L 0.9% saline, and administered as an intravenous administration over 30 minutes. Due to incidence of adverse events at the 30 minute infusion time, a protocol amendment extended the infusion time to 60 minutes during the study.

(5) Measurements and Observations: Monthly evaluations included physical examination, lameness examination, clinical pathology (complete blood count and serum chemistry), owner interview, owner diary, and a record of any additional medications administered during the study.

d. Statistical Methods: A paired t-test with a significance level of 0.1 was used to test the differences between initial and pre-NSAID results, between initial and post-NSAID results, and between initial and one month results for clinical pathology outcomes.

e. Results: A total of 87 horses from Study 0611 were enrolled in Study 0705. An additional 14 horses from Study 0611 were treated with only

one dose of TILDREN and followed for one month. Sixty-one horses completed the 6 month study. Most horses that did not complete the study were lost to follow-up. Three horses withdrew for lack of effectiveness. A total of 250 doses of TILDREN were administered to 97 horses.

(1) Clinical pathology: Five horses had elevated creatinine values following treatment with TILDREN. All of these horses received multiple doses of TILDREN (ranging from 3-5 doses between the two studies). The creatinine values returned to normal prior to the end of the study in three of the five horses. The remaining two horses had persistently elevated creatinine values that were just above the normal reference range. These creatinine values did not trend towards increasing with additional doses of TILDREN.

(2) Clinical pathology pre- and post-NSAID treatment: Clinical pathology data was collected for 36 of 40 horses that were treated with flunixin meglumine for post-TILDREN-infusion colic. Statistically significant elevations in BUN ($p=0.0052$) and creatinine ($p<0.0001$) were seen in the post-NSAID samples. Statistically significant elevation in creatinine was also seen in the pre-NSAID samples ($p=0.0004$). BUN remained elevated as compared to the initial sample for one month following TILDREN and NSAID administration ($p=0.0748$). Twelve out of 36 cases had increased creatinine values that remained within the normal reference range. Nine cases had creatinine values above the normal reference range following treatment with an NSAID. The elevations above normal reference range in creatinine ranged from 2.0-3.5 mg/dL. These values returned to within the reference range by the subsequent visit (within 1 month). Statistically significant elevations in phosphorus ($p=0.0265$) and potassium ($p=0.0047$) were seen in the pre-NSAID samples. Statistically significant elevations in calcium ($p<0.0001$), potassium ($p=0.0029$), magnesium ($p<0.0001$) and SDH (0.0275) were seen in the post-NSAID samples. Magnesium remained elevated at the next month sampling point ($p=0.0054$). Horses did not demonstrate clinical signs associated with these clinical pathology changes, except for one horse that demonstrated signs of hyperkalemia (see Adverse Reactions).

f. Adverse Reactions: See Table 12, for the tabular presentation of the reactions seen in this field safety study. See text for more details.

Table 12. Adverse Reactions in the Open Field Safety Study (0705)

Adverse Reaction	Number of Events Out of 250 Treatments in Open Study (%)
Colic[1]- within 24 hours post-infusion	95 (38%)
Injection site swelling/hematoma (n=218 observations)	7 (3%)
Frequent urination-within 4 hours of infusion	4 (2%)
Muscle fasciculations-within 4 hours of infusion	5 (2%)
Polyuria ± polydipsia	3 (1%)
Fever	1 (<1%)
Gastric ulceration	1 (<1%)
Large Colon Impaction	1 (<1%)
Death	1 (<1%)

[1]defined as having at least one of the following signs: pawing, evidence of pawing, getting up and down, pacing, restlessness, rolling, trying to roll, looking or biting at side, stretching out/straining, kicking at belly/walls, and repeatedly shifting weight behind

(1) Death: A 6-year-old American Quarter Horse gelding developed mild signs of colic at the end of the TILDREN infusion. This was the second dose of TILDREN administered to the horse. The horse received the first dose of TILDREN 1 month earlier. The signs of colic resolved rapidly after NSAID administration. However, several hours later the horse exhibited vague signs of discomfort, including elevated respiratory rate and stretching. Muscle fasciculations and sweating were observed while walking the horse. While standing in the stall, the horse had an elevated heart rate (80 beats/min) and respiratory rate (60 breaths/min). To facilitate nasogastric intubation, 150 mg xylazine was administered intravenously. Within 5 minutes of xylazine administration, the horse became ataxic and collapsed. Resuscitation attempts failed. Blood samples revealed a potassium level of 9.2 mEq/L as well as numerous other abnormalities, including hemoconcentration, elevated serum creatinine (3.2 mg/dL), and elevated serum calcium (14.6 mg/dL). Post-mortem genetic testing of a hair sample determined that the horse was a heterozygote for the gene associated with equine Hyperkalemic Periodic Paralysis (HYPP). The horse was an unknown carrier of the gene and did not have previous history of clinical signs associated with HYPP. There were no gross abnormalities at post mortem. Abnormalities found on histopathology were mild and could not be attributed as cause of death. A urine sample collected from the bladder during necropsy revealed a low specific gravity (1.008) and 1+ protein. A presumptive diagnosis of acute cardiac arrest secondary to hyperkalemia was made.

(2) Colic: Out of 250 doses of TILDREN administered, clinical signs of colic, occurring within 6.25 hours of the infusion, were recorded for 95 (38%) of the treatments. Forty-nine out of 97 horses (51%) treated with at least one dose of TILDREN had clinical signs of colic at least once. In an individual animal, clinical signs of colic did not worsen with

subsequent doses. The time elapsed to onset of clinical signs of colic ranged from 20 minutes before the end of the infusion to 6.25 hours after the end of the infusion. Incidence of colic signs remained higher in the horses administered TILDREN over 30 minutes when compared to the 60 minute group.

(3) Muscle fasciculations: Muscle fasciculations were observed 5 times, or in 2% of doses administered. In one horse, muscle fasciculations observed during the infusion resolved when the rate of infusion was slowed.

(4) Polyuria/Polydipsia: There were 7 reports of increased urination and/or drinking in 5 horses (4 geldings, 1 female), representing 6% of horses and 3% of treatments. One horse had increased urination and drinking reported one day following each of two treatments. A urine sample collected approximately 2.5 hours after the next infusion one month later revealed a specific gravity of 1.010 and no other abnormalities.

(5) Other: Beyond the immediate post-infusion period, lethargy was reported 2 times (1%) and colic with gastric ulceration once (<1%). There were 5 other uncomplicated episodes of colic between visits.

g. Conclusions: Intravenous infusion of TILDREN over 30 or 60 minutes in the field is associated with the development of colic signs up to 6 hours following the infusion, with the 30 minute group being at higher risk of developing colic signs. Treatment of colic signs with NSAIDs may adversely affect renal function. Long term effects on renal function are unknown. Additionally, treatment of horses heterozygous for the Hyperkalemic Periodic Paralysis (HYPP) gene with TILDREN may pose serious risk, including death.

2. Infusion Rate Field Safety Study

a. Title: Complimentary Clinical Field Safety Study: Effect of Infusion Time of 145R1 on Incidence of Colic in Horses. Study number US/CLI/145R1/1201. June-September 2012

b. Investigators:

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Christina Rusillo, DVM
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c. Study design:

(1) Objective: To assess the effect of lengthening the duration of intravenous infusion of TILDREN to 90 and 120 minutes on the incidence of clinical signs consistent with colic.

(2) Study Animals: 137 client-owned horses were enrolled, representing various breeds, 4-27 years of age.

(3) Experimental Design: Horses were randomly assigned to one of two treatment groups, 90 or 120 minute infusion of TILDREN. Horses were administered test article and monitored for 4 hours following the end of infusion. Horse owners were contacted 3-7 days following the infusion to inquire about any potential adverse events that may have occurred.

(4) Drug Administration: Treatment consisted of a single intravenous infusion, of either 90 or 120 minute duration, of TILDREN (tiludronate disodium) diluted in 1 L of 0.9% saline. Dosing was performed using the same dosing chart as that used in previous field studies (See Field Effectiveness), delivering approximately 1 mg/kg body weight.

(5) Measurements and Observations: Baseline physical examination, lameness examination, hematology, and serum chemistry were performed 0-3 days prior to the infusion. Immediately prior to initiation of infusion, horses were observed for at least 30 minutes to establish baseline behavior. Horses were observed continuously during the infusion and for 4 hours following the end of the infusion. If abnormal clinical signs were noted, heart rate, respiratory rate, mucous membrane color, capillary refill time, and results of gastrointestinal auscultation were periodically recorded. Horses were given a colic severity score at the end of the post-treatment period; see Table 13 for the scoring system. If the horse was kept in the veterinary clinic overnight, twice daily clinical observations were made during the hospitalization. Owners were contacted 3-7 days following the infusion date, and were asked about any adverse events that may have occurred.

Table 13. Colic Severity Score

Score	Definition
0	Horse appeared comfortable at all times
1	Resolved with non-medical intervention within 30 minutes (includes hand walking)
2	Resolved with non-medical intervention after longer than 30 minutes (includes hand walking)
3	Required administration of an analgesic (such as BUSCOPAN or alpha-2 agonist $\pm$ opioid)
4	Required repeated administration of analgesics and/or required additional medical intervention (IV fluids, nasogastric intubation, etc)
5	Required extensive medical treatment to resolve colic (repeated analgesics combined with IV fluids, nasogastric intubation, etc) lasting longer than the 4 hour post-treatment period or Required surgical intervention or Death/Euthanasia due to colic

d. Statistical Methods: The experimental unit was the individual horse. The primary safety criterion was the severity score. The incidence of colic in each group was summarized by percent colic at 95% confidence intervals. The incidence of colic was analyzed using a general linear mixed effect model (PROC GLIMMIX in SAS) with a binomial distribution, a logit link, group as a fixed effect, and site and site by group as random effects to test the difference between the two groups. Severity of colic in each group was summarized by frequencies within a severity ranking. No hypothesis testing was conducted for severity.

e. Results: There was no statistically significant difference between groups in the incidence of colic. Sixty horses (44%) showed one or more signs of colic, when compared to the baseline period. Severity of colic appeared to be similar between treatment groups (See Table 14). Twenty-seven horses (45% of horses with colic) were given a colic score of 2. On average, colic signs lasted 90 minutes. This average time includes signs that were intermittent in nature. Seventeen horses (28%) required medical treatment (at least one dose of non-NSAID analgesic or other medication) for colic signs. Fourteen (25%) horses required a single dose of medication to resolve colic signs. Three horses required multiple drugs for resolution of signs. Horses that required medical treatment were mostly treated with non-NSAIDs, including n-butylscopolammonium bromide and alpha-2 agonists with or without an opioid. After multiple doses of other medications (including n-butylscopolammonium bromide, xylazine, and detomidine), one horse required treatment with flunixin meglumine to resolve clinical signs of colic.

Table 14. Severity Scores of Horses with Colic Signs

Severity Score	Number of Horses Exhibiting Colic Signs (90-Minute Infusion Group)	Number of Horses Exhibiting Colic Signs (120-Minute Infusion Group)
1	7	9
2	15	12
3	8	6
4	1	2

f. Adverse Reactions: Most of the adverse events reported had been reported with similar frequency in previous field studies. See Table 15. However, one horse developed anorexia and fever the evening of the TILDREN infusion. The horse was treated with flunixin for fever, and concurrent blood work revealed azotemia. The azotemia initially persisted despite intravenous fluid therapy. The horse was diagnosed with acute renal failure. Over several weeks the horse's renal parameters (BUN/creatinine) returned to within normal limits and the horse did not require further medical therapy.

One horse developed nystagmus and paddling during an episode of colic. Shortly after clinical signs of colic started, the horse was administered BUSCOPAN and xylazine. Clinical signs resolved for approximately 30 minutes, and then the horse's signs of colic returned and included intermittent observations of nystagmus, and one observation of paddling while in lateral recumbency. The clinical signs lasted over 2 hours and no additional medications were administered. Blood work during the episode revealed no significant abnormalities, although ionized calcium was on the low end of the normal reference range. The horse recovered uneventfully without further treatment.

Three days following TILDREN infusion, one horse developed clinical signs of colic that were ultimately attributed to gastric ulcers as diagnosed by gastroscopy.

Table 15. Adverse Reactions During Field Study 1201

Adverse Reaction	Number of Horses (%)
Colic*	60 (44%)
Increased frequency of urination in the immediate post-treatment period (more than 2 times in the 4 hour period)	11 (8%)
Decreased feed intake/anorexia	4 (3%)
Loose stool during infusion (mild, transient)	3 (2%)
Fever	3 (2%)
Depression/lethargy	3 (2%)
Yawning/head shaking/head nodding/head pressing	2 (1%)
Nystagmus and paddling	1 (<1%)
Acute renal failure	1 (<1%)
Gastric ulcers	1 (<1%)

*Determined by the investigator, but including any of the following: pawing, getting up and down, stretching out, circling stall, flank watching, kicking at belly or walls, rolling, and trying to roll.

g. Conclusions: There was no statistical or clinical difference between horses administered TILDREN over 90 or 120 minutes in the incidence of adverse events. Clinical signs of colic occurred in approximately 44% of horses administered TILDREN. Fewer horses were treated with medication for colic signs in this study compared to other field studies, demonstrating that a 90 minute infusion provides an improved safety profile when compared to 60 minute infusion. Additionally, the majority of colic signs may be safely managed either without analgesics or with non-NSAID drug treatments. One horse experienced acute renal failure after concurrent administration of TILDREN and an NSAID. There is an increased risk of renal adverse events when TILDREN is administered concurrently with NSAIDs.

C. Overall Safety Conclusion

Following a review of all available safety information, including the above summarized studies and foreign experience adverse event reports, TILDREN is safe when used according to the label instructions. TILDREN-related clinical signs of colic are well characterized, generally self-limiting, and can be minimized with the use of a slow, evenly administered infusion. In horses that require medical treatment for colic, use of non-NSAID analgesics reduces the risk of renal adverse events. NSAIDs should not be used concurrently with TILDREN. Concurrent use of NSAIDs with TILDREN may increase the risk of renal toxicity and acute renal failure. Caution should be used when administering TILDREN to horses with Hyperkalemic Periodic Paralysis.

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 TILDREN:

"Not for use in humans. Keep this and all medications out of the 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 TILDREN, 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 required to diagnose navicular syndrome, properly administer the intravenous infusion, and to monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity:

TILDREN, 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.