Date of Approval: June 17, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-262

CERENIA

Maropitant Citrate

Tablets

Dogs

This supplement provides for the extension of the number of days of consecutive use from "5 days" to "until resolution of acute vomiting" for the prevention of acute vomiting in dogs 7 months and older.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-262

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

CERENIA

D. Established Name

Maropitant citrate

E. Pharmacological Category

Antiemetic

F. Dosage Form

Tablets

G. Amount of Active Ingredient

16, 24, 60, and 160 mg of maropitant as maropitant citrate per tablet.

H. How Supplied

CERENIA peach-colored tablets are scored with a break line. Each tablet is marked with "MPT" and the tablet strength on one side and the Zoetis logo on the other. Each tablet size is packaged in a bottle containing 60 tablets and packaged in blister packs containing 4 tablets per perforated sheet.

I. Dispensing Status

Rx

J. Dosage Regimen

Prevention of Acute Vomiting in dogs 2 -7 months: Administer CERENIA Tablets orally at a minimum dose of 2 mg/kg (0.9 mg/lb) body weight once daily for up to 5 consecutive days.

Prevention of Acute Vomiting in dogs 7 months and older: Administer CERENIA Tablets orally at a minimum dose of 2 mg/kg (0.9 mg/lb) body weight once daily until resolution of acute vomiting.

Prevention of Vomiting due to motion sickness in dogs 4 months and older: Administer CERENIA Tablets orally at a minimum dose of 8 mg/kg (3.6 mg/lb) body weight once daily for up to 2 consecutive days.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

For the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs.

N. Effect of Supplement

This supplement provides for extension of the number of days of consecutive use from "5 days" to "until resolution of acute vomiting" for the prevention of acute vomiting in dogs 7 months and older.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosages. The Freedom of Information (FOI) Summary for the original approval of NADA 141-262, dated January 29, 2007, contains dosage characterization information for dogs.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-262, dated January 29, 2007, contains a summary of studies that demonstrate effectiveness of the drug for dogs.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

1. Study Title and Number: 3-Month Oral Toxicity Study in Beagle Dogs, 94-1044-11

   a. Type of Study: Laboratory toxicity study conducted according to Good Laboratory Practices

   b. Location: Pfizer Central Research
   Groton, CT

c. General Design

(1) Purpose of Study: This study evaluated the potential oral toxicity of CJ-11,972-27 (maropitant) in Beagle dogs when administered by oral gavage for 3 months.

(2) Description of Test Animals: Twenty four Beagle dogs were enrolled in the study. Body weights ranged from 8.6-11.3 kg for males and 7.1-10.4 kg for females. The dogs were 7 months old when enrolled.

(3) Control and Treatment Groups:

Treatment Group	Dosage (mg/kg/day)	Route	Number and Gender of Animals
1	0 mg/kg	Oral	6 (3M, 3F)
2	1 mg/kg/day	Oral	6 (3M, 3F)
3	5 mg/kg/day	Oral	6 (3M, 3F)
4	20 mg/kg/day	Oral	6 (3M, 3F)

(4) Dosage Form: CJ-11,972-27 with a citrate buffer was formulated into 1 mL/kg solutions for each dose group.

(5) Drug Administration: Dogs were administered CJ-11, 972-27 dissolved in citrate buffer by oral gavage once daily for 93 days. Control dogs were administered citrate buffer vehicle only.

(6) Variables Measured: All dogs were observed at least 5 times daily in their cages for signs of toxicity and for any changes in appearance or behavior. In addition, the following parameters were measured:

(a) Body weight: Weekly

(b) Food consumption: Daily

(c) Ophthalmology: Day 0 and 85

(d) Physical examination/ Electrocardiogram (EKG)/blood pressure (BP): Twice prior to study initiation and Days 23-26, 51-54, and 79-82

(e) Hematology/serum chemistry: Twice prior to study initiation and on days 29, 57, and 88

(f) Urinalysis: Twice prior to study initiation and on day 87

(g) Fecal: Twice prior to study initiation and on day 87

(h) Serum drug concentrations: Blood samples were collected on days 0, 1, 31 and 92

(i) Necropsy: Day 94

(7) Statistical Analysis: For continuous variables observed at multiple post-treatment time points per subject, a repeated measures analysis of covariance (RMANCOVA) model was used with Dose, Sex, Time, Dose-by-Sex, Sex-by-Time, Dose-by-Time, and Dose-by-Sex-by-Time as fixed effects. The pretreatment value closest to first dose was used as a covariate. All tests were performed at alpha=0.10, except for the test for the 3-way interaction. No additional analysis was performed if the 3-way interaction was significant at alpha=0.05. Mean comparisons between each dose group and control within sex, within time or overall were performed to follow up on significant effects. No adjustments were made for multiple comparisons.

For blood pressure and ECG assessments, two assessments were performed within each scheduled week: once just prior to dosing and another at 1.5 hours after dosing. Therefore, the RMANCOVA model included another factor, hour, and all interaction terms that include hour. The analysis used a doubly repeated covariance structure: between observations across weeks, and between repeated assessments within the selected day of that week.

d. Results

(1) Mortality/appearance/behavior: Sporadic occurrences of salivation were observed among both control dogs and dogs administered maropitant, but were generally more prevalent at 20 mg/kg/day. Emesis was observed in two of three females administered maropitant at 20 mg/kg/day on day 1, and occurred sporadically in a few control, 1, and 20 mg/kg/day dogs during the remainder of the study.

Sporadic incidents of loose or watery stools were noted among both control dogs and dogs administered maropitant, but were generally more prevalent in dogs administered maropitant at 20 mg/kg/day.

(2) Body weight: Six (6/6) dogs administered maropitant at 20 mg/kg/day had a decrease in body weight (1.3-15.2%). One dog (1/6) administered maropitant at 5 mg/kg/day had a 7.3% decrease in body weight. Three (3/6) dogs administered maropitant at 1 mg/kg/day had a decrease in body weight (1.2-4.5%). In the control group, one (1/6) dog had a 3% decrease in body weight at the end of the 3 month treatment period.

(3) Food consumption: Some of the dogs administered maropitant at 5 mg/kg/day and all dogs administered 20 mg/kg/day during weeks 1- 4 took longer to eat their daily ration (defined as more than 3 hours). Normal food consumption patterns were observed by day 28 except for sporadic occurrences of prolonged food consumption in some 20 mg/kg/day dogs during the remainder of the study.

(4) Physical examination/vital signs/ophthalmology/blood pressure/urinalysis: There were no treatment-related changes in heart rate, respiratory rate, rectal temperature, ophthalmology, blood pressure, or urinalysis recorded from any dog.

(5) Electrocardiogram (EKG): Changes in EKG parameters were limited to dogs administered maropitant at 20 mg/kg/day. These consisted of trends toward increased P-R interval, P wave duration, and QRS amplitude over the course of drug treatment.

(6) Hematology: Lower mean red cell parameters (red blood cell count, hemoglobin, and hematocrit) and higher platelet counts and reticulocytes were apparent in one female in the 20 mg/kg/day dose group.

(7) Serum chemistry: Mean serum albumin was lower in the 20 mg/kg/day dose group. Mean serum aspartate aminotransferase was higher in the 20 mg/kg/day male dose group.

(8) Serum drug concentrations: Serum drug exposure of maropitant (by Area Under the Curve [AUC]) was supraproportional with increasing dose with no observed sex differences in exposure. Serum AUC values in each dose group increased 1.3 to 2.3-fold between days 1 and 31, with values fairly consistent between days 31 and 92.

(9) Necropsy: Increased cellularity of the bone marrow was observed in one female dog administered maropitant at 20 mg/kg/day. This female dog had also lower red cell parameters with corresponding higher percent reticulocytes. Higher group mean absolute and relative adrenal weights were apparent at 20 mg/kg/day in females. Vacuolation of the zona glomerulosa of both adrenal glands was observed in three of six dogs administered maropitant at 20 mg/kg/day. Vacuolation of the zona fasciculata of both adrenal glands was observed in two of six dogs administered maropitant at 5 mg/kg/day. Lower mean absolute brain weight in females administered maropitant at 20 mg/kg/day was considered to be related to the lack of growth of high dose females when compared to controls.

e. Conclusions: This study supports the safe use of maropitant citrate administered at 2 mg/kg/day in dogs 7 months of age and older for prevention of acute vomiting. The administration of maropitant produced sporadic clinical signs (salivation, emesis), body weight loss, and lower serum albumin levels at a dose of 20 mg/kg/day. Maropitant increased P-R interval, P wave duration, and QRS amplitude over the course of drug administration in the 20 mg/kg/day dose group. One female in the 20 mg/kg/day dose group had increased cellularity of the bone marrow. This female was noted to have lower mean red cell parameters (red blood cell count, hemoglobin, hematocrit) and higher platelet counts and reticulocytes.

B. Pharmacokinetics study (PK):

1. Study Title and Number: Pharmacokinetics of CJ-11972 Dosed Orally to Dogs at 2 and 8 mg/kg Bodyweight for 14 Consecutive Days (Non-GLP), Study#1562R-60-10-A19.

   a. Location: Pfizer Animal Health
      Kalamazoo, MI

   b. General Design

      (1) Purpose of Study: To characterize steady state blood levels and pharmacokinetics (PK) of maropitant (CJ-11972) and metabolite (CJ-18518) following daily oral dose of Cerenia tablet at 2 and 8 mg/kg doses for 14 consecutive days.

      (2) Description of Test Animals: Sixteen Beagle dogs (8 males and 8 females) were enrolled in the study. Body weights of all dogs ranged from 6.5-18.3 kg. Age ranged from 10 months to 5.0 years.

      (3) Treatment Groups:

Treatment Group	Dosage (mg/kg/day)	Route	Number and Gender of Animals
T01	2.0 mg/kg/day for 14 Consecutive days	Oral	8 (4M, 4F)
T02	8 mg/kg/day for 14 Consecutive days	Oral	8 (4M, 4F)

      (4) Dosage Form: CERENIA (maropitant citrate) tablets

      (5) Drug Administration: CERENIA (maropitant citrate) tablets were administered following an overnight fast.

      (6) Variables Measured: Blood samples were collected prior to dosing, then at 0.5, 1, 1.5, 2, 3, 7 and 24 h after the first dose; then 24 h after each of doses 2-13; then at 0.5, 1, 1.5, 2, 3, 7, 24, 31, 48, 55 and 72 h after the last dose.

      (7) PK Analysis: Non-compartmental pharmacokinetic analysis was performed on the plasma concentration data for each analyte after the first and last dose to measure the $AUC_{(0-24)}$. Other parameters estimated include C_t (trough concentration after each dose), C_{max}, T_{max}, and terminal elimination rate constant ($T_{1/2}$, determined after the last dose only). Steady state was determined based on sequential tests for Ct (trough).

   c. Results: Mean C_{max}, AUC and C (troughs) for CJ-11972 and metabolite CJ-18518 increased greater than dose proportionality with an increase in

dose from 2 to 8 mg/kg single and multiple doses. CJ-11972 accumulation was substantially greater after fourteen 8 mg/kg doses than after fourteen 2 mg/kg doses as reflected in an accumulation ratio in $AUC_{(0-24)}$ of 4.81 (95% CI: 3.28, 7.05) at 8 mg/kg and 2.46 (1.68, 3.61) at 2 mg/kg (Table 1). On day 14, mean terminal half-life also increased with increase in dose indicating non-linear kinetics. This nonlinearity is attributed to saturation of metabolism pathway. Steady state determination based on sequential tests for Ct (trough) indicated that the steady state was reached after the 4th dose for CJ-11972 and the 3rd dose for CJ-18518.

Table 1. Mean (±SD) Plasma Pharmacokinetic Parameters for Maropitant (CJ-11972) in Beagle Dogs after single dose and repeat oral doses of Maropitant:

PK Parameter	2 mg/kg Single Dose	2 mg/kg repeat Doses[a]	8 mg/kg Single Dose	8 mg/kg repeat Doses[a]
Tmax[b] (hr)	2.0 (1.5 – 3.0)	1.5 (1.0 – 3.0)	1.5 (1.0 – 3.0)	2.5 (1.5 – 7.0)
Cmax (ng/mL)	154 (111)	304 (165)	588 (416)	1409 (516)
$AUC_{(0-24)}$ (ng*hr/mL)	1440 (982)	3890 (3030)	6730 (5030)	26600 (9200)
$T_{1/2}$[b] (hr)	NC	7.69 (6.21 - 17.8)	NC	25.4 (6.06 - 30.0)
Accumulation Ratio (R_{ac})[c]	NA	2.46 (1.68, 3.61)	NA	4.81 (3.28, 7.05)

[a]Following once daily doses of maropitant (CJ-11972) for 14 days.
[b]Median (Range)
[c]Ratio=Multiple Dose $AUC_{(0-24)}$/Single Dose $AUC_{(0-24)}$, Least square means (95% Confidence Interval)
NA= Not Applicable
NC= Not Calculated

d. Conclusion: In a 14-day repeat dose PK study, mean Cmax, AUC and C (troughs, steady state) for CJ-11972 and metabolite CJ-18518 increased greater than dose proportionality with an increase in dose from 2 to 8 mg/kg single and multiple doses. CJ-11972 accumulation was substantially greater after fourteen 8 mg/kg doses than after fourteen 2 mg/kg doses as reflected in an accumulation ratio in $AUC_{(0-24)}$ of 4.81 (95% CI: 3.28, 7.05) at 8 mg/kg and 2.46 (1.68, 3.61) at 2 mg/kg. The mean $T_{1/2}$ after the 14th dose was 9.22 (5.79, 12.6) hr for 2 mg/kg and 21.7 (3.6, 29.7) hr for 8 mg/kg. These patterns are also reflected in CJ-18518 although to a somewhat lesser extent. The time to reach steady state trough levels of CJ-11972 was approximately 4 doses and 8 doses for daily 2 mg/kg and 8 mg/kg oral dosing, respectively.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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.

V. USER SAFETY

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

Not for use in humans. Keep out of reach of children. In case of accidental ingestion, seek medical advice. Topical exposure may elicit localized allergic skin reactions in some individuals. Repeated or prolonged exposure may lead to skin sensitization. Wash hands with soap and water after administering drug. CERENIA is also an ocular irritant. In case of accidental eye exposure, flush with water for 15 minutes and seek medical attention.

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 CERENIA, when used according to the label, is safe and effective for the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs.

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 and prevent acute vomiting and vomiting due to motion sickness in dogs.

B. Exclusivity

This supplemental approval for CERENIA qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety studies. This exclusivity begins as of the date of this letter and only applies to extending the number of days of consecutive use from "5 days" to "until resolution of acute vomiting" for the prevention of acute vomiting in dogs 7 months and older.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

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