Date of Approval: January 11, 2016

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-263

CERENIA

(maropitant citrate)

Injectable Solution

Dogs and Cats

This supplement provides for the addition of the intravenous route of administration for dogs and cats, and clarifies the timing of administration prior to use of emetogenic medications in dogs.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-263

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

Injectable solution

G. Amount of Active Ingredient

Each mL contains 10 mg of maropitant as maropitant citrate

H. How Supplied

CERENIA Injectable Solution is supplied in 20 mL amber glass vials

I. Dispensing Status

Rx

J. Dosage Regimen

Use of refrigerated product may reduce the pain response associated with subcutaneous injection.

Dogs:
For Prevention and Treatment of Acute Vomiting in Dogs
Dogs 2-4 Months of Age: Administer CERENIA Injectable Solution subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 0.1 mL/kg (0.1 mL/2.2 lb) of body weight once daily for up to 5 consecutive days.

Dogs 4 months of Age and Older: Administer CERENIA Injectable Solution intravenously over 1-2 minutes or subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 0.1 mL/1 kg (1 mL/22 lb) of body weight once daily for up to 5 consecutive days.

In dogs that are actively vomiting, it is recommended to initiate treatment with CERENIA Injectable Solution. Thereafter, CERENIA Tablets may be used for the prevention of acute vomiting at 2 mg/kg once daily. (See CERENIA Tablets package insert for complete prescribing information.)

For Prevention of Vomiting in Dogs 4 months of Age and Older Caused by Emetogenic Medications or Chemotherapeutic Agents: Administer CERENIA Injectable Solution intravenously over 1-2 minutes or subcutaneously at 1 mg/kg (0.45 mg/lb) of body weight one time, 45-60 minutes prior to use of emetogenic medications or chemotherapeutic agents.

Cats:
For Treatment of Vomiting in Cats 4 Months of Age and Older: Administer CERENIA Injectable Solution intravenously over 1-2 minutes or subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 0.1 mL/kg (0.1 mL/2.2 lb) of body weight once daily for up to 5 consecutive days.

The underlying cause of acute vomiting should be identified and addressed in dogs and cats that receive CERENIA Injectable Solution. If vomiting persists despite treatment, the case should be re-evaluated.

K. Route of Administration

Subcutaneous and intravenous injection

L. Species/Class

Dogs and Cats

M. Indication

Dogs: CERENIA (maropitant citrate) Injectable Solution is indicated for the prevention and treatment of acute vomiting in dogs.

Cats: CERENIA (maropitant citrate) Injectable Solution is indicated for the treatment of vomiting in cats.

N. Effect of Supplement

This supplement provides for the addition of the intravenous route of administration for dogs and cats, and clarifies the timing of administration prior to use of emetogenic medications in dogs.

II. EFFECTIVENESS

The Freedom of Information (FOI) Summary for the original approval of NADA 141-263, dated January 29, 2007, contains the dosage characterization information and a summary of studies that demonstrate effectiveness of the drug for the prevention and treatment of acute vomiting in dogs. The FOI Summary for the supplemental approval of NADA 141-263, dated May 16, 2012, contains the dosage characterization information and a summary of the studies that demonstrate effectiveness of the drug for the treatment of vomiting in cats.

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage.

B. Substantial Evidence

Laboratory Effectiveness Study in Dogs

1. Study Title and Number: Efficacy and Safety of CERENIA Injectable Solution for Prevention of Perioperative Nausea and Vomiting in Dogs Undergoing Routine Surgery (Study #1961R-60-11-A81).

2. Type of Study: Laboratory study

3. Study Dates: May 11-27, 2011

4. Location: Pfizer Animal Health, Kalamazoo, MI

5. General Design:

   a. Purpose of Study: To demonstrate the antiemetic effect of maropitant when administered to dogs prior to administration of the opioid analgesic morphine.

   b. Study Animals: Sixteen male and 16 female dogs, 7-8 months old, weighing 6.8 to 11.1 kg.

   c. Treatment Groups:

Table 1. Treatment Groups

Treatment Groups	Dosage	Number of Animals
T01- Saline (Placebo)	0.1 mL/kg SC[a]	8 males, 8 females
T02- CERENIA Injectable Solution	1 mg/kg SC	8 males, 8 females

[a] Subcutaneous (SC)

CERENIA Injectable Solution or Saline was administered 45 minutes before morphine administration.

d. Masking: Persons conducting clinical observations and collecting data were masked to treatment group assignment.

e. Inclusion/Exclusion Criteria: Dogs were determined to be healthy based on physical examination, Complete Blood Count (CBC), and serum chemistry.

f. Dose Administration: CERENIA Injectable Solution (1 mg/kg) or saline (0.1 mL/kg) was administered subcutaneously 45 minutes before administration of morphine (0.5 mg/kg) subcutaneously for analgesia. Morphine was administered approximately 30 minutes prior to anesthesia induction.

g. Measurements and Observations: Number of emetic events after morphine administration.

h. Statistical Methods: Presence of emetic events was summarized by treatment and time point. Whether or not an animal had an emetic event up to 150 minutes into recovery was summarized by treatment and sex. Whether or not an animal had an emetic event was analyzed using Fisher's Exact Test as the generalized linear mixed model with a logit link function and a binomial error distribution did not converge.

i. Criteria for Success/Failure: The primary effectiveness parameter was the number of emetic events.

6. Results

a. Emetic Events: CERENIA Injectable Solution was significantly different from saline ($p < 0.05$) for prevention of morphine induced vomiting. No CERENIA Injectable Solution group dogs vomited, and 15 of 16 (93.8%) saline-treated dogs vomited at 5 or 10 minutes after morphine administration. Of the 14 saline-treated dogs with emetic events, 5 dogs vomited once, 5 dogs vomited twice, and 4 dogs vomited three times.

Table 2. Summary of Number (Percent) of Dogs with Emetic Events by Treatment Group and Time Period

Time Period (minutes)	CERENIA T02 n (%)[a]	Saline T01 n (%)
-75	0 (0)	0 (0)
-25	0 (0)	14 (87.5)
-20	0 (0)	4 (25)
-15	0 (0)	0 (0)
-10	0 (0)	0 (0)
-5	0 (0)	0 (0)
At induction	0 (0)	0 (0)
At extubation	0 (0)	0 (0)
Post-extubation[b]	0 (0)	0 (0)

[a] One treated dog that received a partial dose of CERENIA was removed from the statistical analysis.
[b] From +15 minutes after extubation up to 150 minutes

7. Adverse Reactions: None reported.

8. Conclusions: CERENIA Injectable Solution administered at 1 mg/kg subcutaneously, 45 minutes before morphine administration, was effective in the prevention of morphine-induced vomiting. No adverse events were observed during the study.

Pharmacokinetic Study in Dogs

1. Study Title and Number: Absolute Bioavailability of CJ-11972 in Dogs Using Commercially Available CERENIA Injectable Solution (Study #A461N-US-13-289).

2. Type of Study: Laboratory study conducted according to GLP

3. Study Dates: October 28- November 16, 2013.

4. Location: Covance Laboratories, Madison Wisconsin

5. General Design:

   a. Purpose of Study: To estimate the absolute bioavailability of maropitant (CJ-11972) in dogs after administration of 1.0 mg/kg Intravenous (IV) or 1.0 mg/kg Subcutaneous (SC) in a two treatment, two period cross-over study.

b. Study Animals: Four male and 4 female Beagle dogs, 9 months to 3 years old, weighing 9.3-11.5 kg.

c. Treatment Groups:

Table 3. Treatment Groups

Sequence	Period 1	Period 2	Number of Animals Per Sequence
1	1.0 mg/kg IV	1.0 mg/kg SC	2 males, 2 females
2	1.0 mg/kg SC	1.0 mg/kg IV	2 males, 2 females

There was an approximately 17 day washout period between Sequence 1 and 2.

d. Masking: There was no masking. Blood samples were identified with the study number, sponsor reference number, period, animal ID, matrix, aliquot designation (primary or back-up) and collection time point. The route of administration was not included on the samples.

e. Inclusion/Exclusion Criteria: Dogs were determined to be healthy based on physical examination, CBC, and serum chemistry.

f. Dose Administration: Animals were not fasted prior to dosing. The SC dose was administered via a needle and syringe into tented skin in the dorso-scapular region. The IV dose was administered via a cephalic vein catheter as a bolus injection.

g. Parameters Measured: For each period, blood samples were collected at 0 (pre-dose), 0.05 (3 minutes), 0.25, 0.5, 1, 1.5, 2, 3, 6, 8, 24, and 48 hours post-dose. Sampling times were ± 10% to a maximum of ± 20 minutes. Concentrations of maropitant (CJ-11972) and the metabolite CJ-18518 in plasma were measured using a validated LC-MS/MS method.

h. Pharmacokinetic and Statistical Methods: Non-compartmental pharmacokinetic parameters were determined for each dog using Phoenix 64 WinNonlin version 6.3 (Pharsight Corp.) The AUC_{last} was estimated using the linear trapezoidal method. The C_{max} was the highest observed plasma concentration for each dog. C_{max} and AUC_{last} were logarithmically transformed prior to bioequivalence analysis. The mean IV and SC pharmacokinetic parameters (± standard deviation, SD) are summarized in Table 4.

Table 4: Mean (± SD) PK parameters of maropitant (CJ-11972) after IV and SC administration of a single dose of 1.0 mg/kg maropitant in a 2 treatment, 2 period crossover study in dogs

Route	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	Half-life (hr)	Vd_{ss} (L/kg)	CL (mL/hr/kg)
IV	296.62 (60.77)	n/a	675.40 (139.94)	693.83 (137.25)	6.85[a] (2.13)	9.63 (2.53)	1499.13 (345.40)
SC	102.99 (46.06)	0.56 (.40)	733.11 (198.77)	759.08 (189.49)	8.84[a] (4.78)	n/a	n/a

[a] Harmonic mean
C_{max}= maximum plasma concentration
T_{max}= time to maximum plasma concentration
AUC_{last} = area under the plasma time vs concentration curve to the last quantifiable time point at 32 hours for IV and 48 hours for SC
AUC_{inf}= area under the plasma time vs concentration curve extrapolated to infinity
Vd_{ss}= volume of distribution at steady state
CL= clearance

6. Results: The bioavailability of the SC route of administration exceeded 100% (109%), which could be attributable to the inherent variability of maropitant and/or an underestimation of the extrapolated initial concentration of the IV route of administration. The IV route of administration resulted in a substantially higher C_{max}, but the AUC_{last} of both routes were bioequivalent (geometric treatment mean 0.93; 90% CI of 85.81- 100.51%). The therapeutic equivalence of the higher C_{max} was supported by data from radiolabeled, dose determination, and absolute bioavailability studies, in addition to information from the scientific literature.

   The maropitant brain concentrations from a radiolabelled study (Study 1565R-60-09-937) and a pharmacokinetic/pharmacodynamic (PK/PD) model (Study 561C-12-01-241) were used as justification that the shorter IV half-life would not negatively impact effectiveness at 24 hours. Data from the IV target animal safety study, A366N-US-13-276, (See Target Animal Safety) demonstrated that the higher maropitant concentrations did not increase the magnitude of drug accumulation, and both routes of administration resulted in similar AUCs at steady state. These data also demonstrated that the IV administration did not substantially alter the rate of clearance of maropitant. Information from the scientific literature was also used to support the therapeutic equivalence of the IV administration. In a study comparing two formulations of another NK-1 antagonist[1], the AUC was the parameter of interest for effectiveness.

   [1] Lasseter K. et al (2007), Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. Journal of Clinical Pharmacology, 47, 834-840.

7. Conclusions: The IV and SC administration of a single dose of 1.0 mg/kg maropitant are equivalent, based on the bioequivalence of the IV and SC AUC_{last} and justification for the therapeutic equivalence of the IV and SC C_{max}.

Pharmacokinetic Study in Cats

1. Study Title and Number: Absolute Bioavailability of CJ-11972 in Cats Using Commercially Available CERENIA Injectable Solution (Study #A481N-US-13-080).

2. Type of Study: Laboratory study conducted according to GLP

3. Study Dates: November 14 through December 15, 2013.

4. Study Location: Covance Laboratories, Madison Wisconsin

5. General Design:

   a. Purpose of Study: To estimate the absolute bioavailability of maropitant (CJ-11972) in cats after administration of 1.0 mg/kg IV or 1.0 mg/kg SC in a two treatment, two period cross-over study.

   b. Study Animals: Four male and 4 female cats, 6-7 months old, weighing 2.2-4.4 kg.

   c. Treatment Groups:

      Table 5. Treatment Groups

Sequence	Period 1	Period 2	Number of Animals Per Sequence
1	1.0 mg/kg IV	1.0 mg/kg SC	2 males, 2 females
2	1.0 mg/kg SC	1.0 mg/kg IV	2 males, 2 females

      There was an approximately 21 day washout period between Sequence 1 and 2.

   d. Masking: There was no masking. Blood samples were identified with the study number, sponsor reference number, period, animal ID, matrix, aliquot designation (primary or back-up) and collection time point. The route of administration was not included on the samples.

   e. Inclusion/Exclusion Criteria: Cats were determined to be healthy based on physical examination, CBC, and serum chemistry. Two cats (1 male and 1 female) were eliminated from the IV analysis because of extravascular dose administration.

   f. Dose Administration: Animals were not fasted prior to dosing. The SC dose was administered via a needle and syringe into tented skin in the dorso-scapular region. The IV dose was administered via a cephalic vein catheter as a bolus injection.

   g. Parameters Measured: For each period, blood samples were collected at 0 (pre-dose), 0.05 (3 minutes), 0.25, 0.5, 1, 1.5, 3, 8, 24, 32, 48, 72, 120, 168, and 240 hours post-dose. Sampling times were ± 10% to a maximum of ± 20 minutes. Concentrations of maropitant (CJ-11972) and

the metabolite CJ-18518 in plasma were measured using a validated LC-MS/MS method.

h. Pharmacokinetic and Statistical Methods: Non-compartmental pharmacokinetic parameters were determined for each cat using Phoenix 64 WinNonlin version 6.3 (Pharsight Corp.) The AUClast was estimated using the linear trapezoidal method. The Cmax was the highest observed plasma concentration for each cat. Cmax and AUClast were logarithmically transformed prior to bioequivalence analysis. The mean IV and SC pharmacokinetic parameters (± standard deviation, SD) are summarized in Table 6.

Table 6: Mean (± SD) PK parameters of maropitant (CJ-11972) after IV and SC administration of a single dose of 1.0 mg/kg maropitant in a 2 treatment, 2 period crossover study in cats

Route	C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	Half-life (hr)	Vd_{ss} (L/kg)	CL (mL/hr/kg)
IV	987.65 (421.75)	n/a	2095.99 (704.39)	2116.53 (706.72)	4.86[a] (1.22)	2.31 (0.78)	509.23 (133.74)
SC	257.84 (49.95)	0.43 (0.33)	1994.19 (515.01)	2016.07 (516.65)	6.57[a] (1.52)	n/a	n/a

[a] Harmonic mean
C_{max}= maximum plasma concentration
T_{max}= time to maximum plasma concentration
AUC_{last} = area under the plasma time vs concentration curve to the last quantifiable time point at 32 hours for IV and 48 hours for SC
AUC_{inf}= area under the plasma time vs concentration curve extrapolated to infinity
Vd_{ss}= volume of distribution at steady state
CL= clearance

6. Results: The IV route of administration resulted in a substantially higher C_{max}, but the AUC_{last} of both routes were bioequivalent (geometric treatment mean 1.05; 90% CI of 89.37- 124.33%). The therapeutic equivalence of the higher C_{max} was supported by data from radiolabeled, dose determination, and absolute bioavailability studies, in addition to information from the scientific literature.

   The maropitant brain concentrations from a radiolabelled study (Study A482R-US-12-010) were used as justification that the shorter IV half-life would not negatively impact effectiveness at 24 hours. Data from the IV target animal safety study, A386N-US-13-077, (See Target Animal Safety) demonstrated that the higher maropitant concentrations did not increase the magnitude of drug accumulation, and both routes of administration resulted in similar AUCs at steady state. These data also demonstrated that the IV administration did not substantially alter the rate of clearance of maropitant. Information from the scientific literature was also used to support the therapeutic equivalence of the IV administration. In a study comparing two formulations of another NK-1 antagonist [1], the AUC was the parameter of interest for effectiveness. The effectiveness of the IV route of administration was also supported by a study conducted in cats administered xylazine as an emetogen.[1,2]

[2] Hickman, M.A. et al. (2008), Safety, pharmacokinetics, and use of the novel NK-1 receptor antagonist maropitant (Cerenia) for the prevention of emesis and motion sickness in cats. Journal of Veterinary Pharmacology and Therapeutics, 31, 220-229.

7. Conclusions: The IV and SC administration of a single dose of 1.0 mg/kg maropitant are equivalent, based on the bioequivalence of the IV and SC AUC_{last} and justification for therapeutic equivalence of the IV and SC C_{max}.

III. TARGET ANIMAL SAFETY

A. Multi-dose Intravenous Safety Study in Dogs

1. Study Title and Number: A 5-Day Intravenous (Bolus) Injection Safety Study of CJ-11,972 in Beagle Dogs. (Study #: A366N-US-13-276).

2. Type of Study: Laboratory study conducted according to GLP

3. Study Dates: October 16, 2013-May 2, 2014.

4. Study Location: WIL Research, Ashland, Ohio

5. General Design:

   a. Purpose of Study: The objective was to evaluate the safety of CERENIA Injectable Solution (maropitant citrate) when administered intravenously at 1X and 3X the labeled dose for 5 consecutive days to Beagle dogs. The study focused on post-administration clinical signs, the route of administration, and bone marrow.

   b. Study Animals: The study included 24 healthy Beagle dogs (12 males and 12 females), aged 16 weeks old on study day 0. There were 8 dogs per treatment group (4 males and 4 females). Male dogs weighed 3.3-5.3 kg and female dogs weighed 3.2-4.3 kg on Study Day 0. Dogs were determined to be healthy based on clinical pathology and physical examination.

   c. Treatment Groups: Dogs were randomized to receive saline (0.9% sodium chloride, USP) or maropitant citrate (1 mg/mL). The study was not masked.

Table 7: Treatment Groups for Dog Intravenous Laboratory Study

Group	Dose mg/kg	Dose Multiple	Dose Volume	Number of Animals
T01	Sterile Saline	0X	0.3 mL/kg	4 males 4 females
T02	Maropitant citrate 1 mg/kg	1X	0.1 mL/kg	4 males 4 females
T03	Maropitant citrate 3 mg/kg	3X	0.3 mL/kg	4 males 4 females

d. Dose Administration: The dose was administered by intravenous injection of 1-2 minutes through a 25G butterfly catheter in the left cephalic vein, once daily for 5 consecutive days. Injection sites were shaved and marked.

e. Study Schedule: Dogs were acclimated for 4 weeks prior to study start. Body weights were recorded weekly during acclimation, on the day of randomization, and on days 0 and 4. Observations for morbidity and mortality were made twice daily. Food consumption was recorded daily from acclimation to study day 4. Detailed physical examination and body weight were conducted on day 0 and at study end. Veterinary physical examinations were conducted on days -3 and 5. Clinical pathology was conducted on days -6 and 5. All dogs were dosed once daily for 5 days (study days 0-4). General health observations were recorded prior to dosing and 15 minutes (± 5 minutes after dosing). Toxicokinetic samples were collected on days 0 and 4 at 3 minutes, 1, 8, and 24 hours post dose. Necropsy was conducted on day 5.

f. Measurements and Observations: Survival (morbidity/mortality), daily general health observations, detailed physical examination, veterinary physical examination, body weight, food consumption, clinical pathology, hematology, coagulation, serum chemistry, plasma toxicokinetic data, gross pathology, macroscopic examination, and histopathology. The study did not include urinalysis. Presence or absence of reaction to injection was not recorded for each dog at every dose administration.

g. Statistical Methods: For food consumption, a repeated measures analysis of covariance (RMANCOVA) model was used with treatment, sex, day, treatment-by-sex, sex-by-day, treatment-by-day, and treatment -by-sex-by-day as fixed effects, and block within sex as a random effect. The average daily food consumption on a 4-day pre-treatment period were used as a covariate and remained in the model regardless of statistical significance. All tests were performed at alpha=0.10, except for the test for the 3-way interaction, which was performed at alpha=0.05. No additional analysis was performed if the 3-way interaction was significant. The Compound Symmetry (CS) covariance function was used to model the correlation between repeated measurements on the same subject. To evaluate significant effects involving treatment, mean comparisons between each treatment group (1X, and 3X) and control were performed (within sex, within time or overall). No adjustments were made for multiple comparisons.

Individual body weight and clinical pathology data were analyzed using a general linear mixed model. The model includes treatment, sex and treatment by sex interaction as fixed effects and block within sex as a random effect. All tests were performed at alpha=0.10. To evaluate significant effects involving treatment, mean comparisons between each treatment group (1X, and 3X) and control were performed (within sex or overall). No adjustments were made for multiple comparisons.

6. Results:

   a. Survival: All dogs survived the study.

   b. General Health Observations and Examinations: There were sporadic incidences of diarrhea and soft stool in all groups. One male in group T01 and one female in group T02 vomited on study day 4. One female in group T03 had injected sclera on study day 2.

   c. Body Weight: There were no statistically significant or clinically relevant effects on body weight.

   d. Food Consumption: There were no clinically relevant differences in food consumption during the dosing phase between the treatment groups.

   e. Clinical Pathology:

      Hematology
      In all groups there was a trend of decreasing white blood cell count and hematocrit. One male dog in group T02 had a normal complete blood count at acclimation, but a decreased white blood cell count (5.03 1000/µL, reference range 6.08-15.05 1000/µL) accompanied by a neutropenia and leukopenia and a decreased hematocrit (37.4%, reference range 37.5-52.8%) on study day 5.

      Serum Chemistry
      There were no clinically relevant differences in serum chemistry variables between the treatment groups.

      Coagulation
      One female dog in group T03 had an increase in fibrinogen on study day 5 (345 mg/dL, with reference range of 132-320 mg/dL).

   f. Necropsy Examination: Dark red areas or discolorations were noted at the cephalic vein injections sites in both the saline and maropitant group dogs. This finding was consistent with the process of administering an intravenous injection, and was not considered test-article related. There were no other procedure-related or test article-related gross necropsy findings. Organ weights were not documented.

   g. Histopathology: There were no test-article associated abnormalities on histopathology. Dogs from all treatment groups had subacute inflammation and hemorrhage at injection sites that was secondary to the intravenous injection procedure.

   h. Plasma Toxicokinetic Analysis: Table 8 below contains the Mean (Standard Deviation) plasma pharmacokinetic parameters for CJ-11972 (maropitant) and CJ-18518 (major active metabolite) following single (day 0) and 5 consecutive (day 4) intravenous injections of 1 mg/kg/day and 3 mg/kg/day CERENIA Injectable Solution (maropitant citrate).

Table 8. Mean (SD) plasma pharmacokinetic parameters for CJ-11972 (maropitant) and CJ-18518 (metabolite) in Dogs

Study Day	Parameter	CJ-11972 in Group T02 (1mg/kg)	CJ-11972 in Group T03 (3 mg/kg)	CJ-18518 in Group T02 (1 mg/kg)	CJ-18518 in Group T03 (3 mg/kg)
0	T_{max} hr	0.05 (0.0)	0.05 (0.0)	1.0 (0.0)	1.0 (0.0)
0	C_{max} ng/mL	297 (33.8)	1040 (232)	32.5 (22.9)	125 (39.0)
0	AUC_{0-t} ng*hr/mL	765 (157)	3080 (616)	223 (124)	959 (269)
4	T_{max} hr	0.05 (0.0)	0.05 (0.0)	1.0 (0.0)	1.0 (0.0)
4	C_{max} ng/mL	328 (44.6)	965 (279)	50.3 (22.3)	118 (32.6)
4	AUC_{0-t} ng*hr/mL	972 (236)	3340 (824)	340 (167)	1110 (375)

C_{max}= maximum plasma concentration
T_{max}= time to maximum plasma concentration
AUC_{0-t} = area under the plasma time vs. concentration curve to the last quantifiable time point [for Day 4 AUC_{0-t}=AUC_{tau}, where tau=dosing interval (24 hour)]

There were no gender differences in the plasma pharmacokinetic parameters of maropitant and a major active metabolite CJ-18518 following a single dose (Day 0) and 5 consecutive daily doses (Day 4) of 1 mg/kg/day (group T02) and 3 mg/kg/day (group T03). On Day 0 and Day 4, mean maropitant T_{max} was similar (0.05 hr) for both the treatment groups. Plasma exposure (C_{max} and $AUC_{(0-t)}$) of maropitant and metabolite CJ 18518 did not increase proportional to dose. On day 0, the mean maropitant C_{max} and AUC_{0-t} for group T03 was 3.5-fold and 4.0-fold greater, respectively, compared to group T02. On day 4, the mean maropitant C_{max} and AUC_{0-t} for group T03 was 2.9-fold and 3.4-fold greater, respectively, compared to group T02. Similar increases in C_{max} and AUC_{0-t} were observed for major metabolite CJ 18518. On day 0, the mean CJ 18518 C_{max} and AUC_{0-t} for group T03 was 3.6-fold and 4.3-fold greater, respectively, compared to group T02. On day 4, the mean CJ 18518 C_{max} and AUC_{0-t} for group T03 was 2.4-fold and 3.3-fold greater, respectively, compared to group T02. On Day 0 and Day 4, mean CJ 18518 T_{max} was similar and occurred at 1.0 hr for both groups (T02 and T03). There was no significant accumulation of maropitant or metabolite CJ 18518 after 5 consecutive daily IV doses of Cerenia Injectable Solution in both treatment groups. The antiemetic activity of the CJ-18518 is limited as it has been shown to minimally cross the blood brain barrier (Study 1565R-60-09-937).

7. Conclusions: The study results support an adequate safety profile for maropitant citrate when administered at 1 mg/kg by IV injection once daily for 5 consecutive days in dogs.

B. Multi-dose Intravenous Safety Study in Cats

1. Study Title and Number: A 5-Day Intravenous (Bolus) Injection Safety Study of CJ-11,972 in Domestic Cats. (Study # A386N-US-13-077).

2. Type of Study: Laboratory study conducted according to GLP

3. Study Dates: October 16, 2013 – May 2, 2014

4. Study Location: WIL Research, Ashland, OH

5. General Design:

   a. Purpose of Study: The objective was to evaluate the safety of CERENIA Injectable Solution (maropitant citrate) when administered intravenously at 1X and 3X the labeled dose for 5 consecutive days to domestic short haired cats. The study focused on post-administration clinical signs, the route of administration, and bone marrow.

   b. Study Animals: The study included 24 healthy domestic shorthair cats (12 males and 12 females), aged 16 weeks old on study day 0. There were 8 cats per treatment group (4 males and 4 females). Male cats weighed 1.89-2.38 kg and female cats weighed 1.39-1.99 kg on Study Day 0. Cats were determined to be healthy based on clinical pathology and physical examination.

   c. Treatment Groups: Cats were randomized to receive saline (0.9% sodium chloride, USP) or maropitant citrate (1 mg/mL).

Table 9. Treatment Groups for Cat Intravenous Laboratory Study

Group	Dose mg/kg	Dose Multiple	Dose Volume	Number of Animals
T01	Sterile Saline	0X	0.3 mL/kg	4 males 4 females
T02	Maropitant citrate 1 mg/kg	1X	0.1 mL/kg	4 males 4 females
T03	Maropitant citrate 3 mg/kg	3X	0.3 mL/kg	4 males 4 females

d. Dose Administration: The dose was administered by intravenous injection over 1-2 minutes through a 25G butterfly catheter in the right cephalic vein, once daily for 5 consecutive days. Injection sites were shaved and marked.

e. Study Schedule: Cats were acclimated for at least 3 weeks prior to study start. Body weights were recorded weekly during acclimation, on the day of randomization, and on days 0 and 4. Observations for morbidity and mortality were made twice daily. Food consumption was recorded daily from acclimation to study day 4. Detailed physical examination and body weight were conducted on day 0 and at study end. Veterinary physical examinations were conducted on days -4 and 5. Clinical pathology was conducted on days -8 and 5. All cats were dosed once daily for 5 days (study days 0-4). General health observations were recorded prior to dosing and 15 minutes (± 5 minutes after dosing). Toxicokinetic samples were collected on days 0 and 4 at 3 minutes, 1, 8 and 24 hours post dose. Necropsy was conducted on day 5.

f. Measurements and Observations: Survival (morbidity/mortality), daily general health observations, detailed physical examination, veterinary physical examination, body weight, food consumption, clinical pathology, hematology, coagulation, serum chemistry, plasma toxicokinetic data, gross pathology, macroscopic examination, and histopathology. The study did not include urinalysis. Presence or absence of reaction to injection was not recorded for each cat at every dose administration.

g. Statistical Methods: For average daily food consumption over the 5-day treatment phase, a repeated measures analysis of covariance (RMANCOVA) model was used with treatment, sex, time, and treatment-by-sex sex-by-time, treatment-by-time, and treatment-by-sex-by-time as fixed effects, and block with sex and error as random effects. The average daily food consumption on a 4-day pre-treatment period was used as a covariate and remained in the model regardless of statistical significance. All tests were performed at alpha=0.10, except for the test for the 3-way interaction, which was performed at alpha=0.05. No additional analysis was performed if the 3-way interaction was significant. The Compound Symmetry (CS) covariance function was used to model the correlation between repeated measurements on the same subject. To evaluate significant effects involving treatment, mean comparisons between each treatment group (1X, and 3X) and control were performed (within sex, within time or overall). No adjustments were made for multiple comparisons.

Individual clinical pathology data were analyzed using a general linear mixed model. Body weight and clinical pathology data collected prior treatment were used as covariates for their respective analyses. The model included treatment, sex and treatment by sex interaction as fixed effects and block within sex as a random effect. All tests were performed at alpha=0.10. If the treatment by sex interaction was not significant but the treatment effect was significant at the 10% level, the treatment LS means were calculated and pairwise comparisons between control and treatments were performed at the unadjusted 10% level of significance.

If no treatment related effects were significant, treatment least squares means were presented but no treatment comparisons were performed. Data may have been transformed to better meet the assumptions of the analysis of variance.

6. Results

   a. Survival and Examinations: All cats survived the study. There were no abnormal physical examination findings in the maropitant citrate and saline groups during the study.

   b. General Health Observations: One male cat in group T02 had soft feces approximately 15 minutes after dose administration. One female cat in group T03 struggled when some of the dose was administered extravascular.

   c. Body Weight: There were no statistically significant or clinically relevant effects on body weight.

   d. Food Consumption: There were no clinically relevant differences in food consumption during the dosing phase between the treatment groups.

   e. Clinical Pathology:

      Hematology
      There were no clinically relevant differences between the treatment groups for hematology variables.

      Serum Chemistry
      There were no clinically relevant differences in serum chemistry variables between the treatment groups.

      Coagulation
      There were no clinically relevant findings on the coagulation profile for prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen.

   f. Necropsy Examination: Dark red areas or discolorations were noted at the cephalic vein injections sites in both the saline and maropitant group cats. This finding was consistent with the process of administering an intravenous injection, and was not considered test-article related. There were no other procedure-related or test article-related gross necropsy findings. Organ weights were not documented.

   g. Histopathology: There were no test-article associated abnormalities on histopathology. Cats from all treatment groups had subacute inflammation and hemorrhage at injection sites that was secondary to the intravenous injection procedure.

h. Plasma Toxicokinetic Analysis: Table 10 below contains the Mean (Standard Deviation) plasma pharmacokinetic parameters for CJ-11972 (maropitant) and CJ-18518 (major active metabolite) following single (day 0) and 5 consecutive (day 4) intravenous injections of 1 mg/kg/day and 3 mg/kg/day CERENIA Injectable Solution (maropitant citrate).

Table 10. Mean (SD) plasma pharmacokinetic parameters for CJ-11972 (maropitant) and CJ-18518 (metabolite) in Cats

Study Day	Parameter	CJ-11972 in Group T02 (1mg/kg)	CJ-11972 in Group T03 (3 mg/kg)	CJ-18518 in Group T02 (1 mg/kg)	CJ-18518 in Group T03 (3 mg/kg)
0	T_{max} hr	0.05 (0.0)	0.05 (0.0)	3.6 (3.6)	3.6 (3.6)
0	C_{max} ng/mL	466 (93.1)	1190 (378)	146 (50.4)	314 (85.7)
0	AUC_{0-t} ng*hr/mL	1500 (310)	3480 (1120)	2390 (855)	4660 (1640)
4	T_{max} hr	0.05 (0.0)	0.05 (0.0)	2.8 (3.2)	2.8 (3.2)
4	C_{max} ng/mL	637 (236)	1450 (309)	249 (106)	425 (120)
4	AUC_{0-t} ng*hr/mL	2080 (683)	4400 (1630)	4410 (2100)	7050 (3250)

C_{max}= maximum plasma concentration
T_{max}= time to maximum plasma concentration
AUC_{0-t} = area under the plasma time vs. concentration curve to the last quantifiable time point [for Day 4 AUC_{0-t}=AUC_{tau}, where tau=dosing interval (24 hour)]

There were no gender differences in the plasma pharmacokinetic parameters of maropitant and the major active metabolite CJ-18515 following a single dose (Day 0) and 5 consecutive daily doses (Day 4) of 1 mg/kg/day (group T02) and 3 mg/kg/day (group T03). On Day 0 and Day 4, following IV dosing, maropitant T_{max} occurred at the first sample time (0.05 hr) for all animals in both dose groups. The increase in C_{max} and AUC_{0-t} were less than dose proportional for both maropitant and the metabolite. On day 0, the mean maropitant C_{max} and AUC_{0-t} for group T03 was 2.6-fold and 2.3-fold greater, respectively, compared to group T02. On day 4, the mean maropitant C_{max} and AUC_{0-t} for group T03 was 2.3-fold and 2.1-fold greater, respectively, compared to group T02. Similar increases in C_{max} and AUC_{0-t} were observed for the metabolite CJ-18518. On day 0, the mean CJ-18518 C_{max} and AUC_{0-t} for group T03 was 2.2-fold and 2.0-fold greater, respectively, compared to group T02. On day 4, the mean CJ-18518 C_{max} and AUC_{0-t} for group T03 was 1.7-fold and 1.6-fold greater, respectively, compared to group T02. On day 0, mean CJ-18518 T_{max} occurred at 3.6 hours for both groups (T02 and T03). On day 4, mean T_{max} occurred at 2.8 hours for both the groups (T02 and T03).

There was moderate accumulation of maropitant and the metabolite after repeat intravenous doses of CERENIA Injectable Solution in both treatment groups. The accumulation ratio for T02 and T03 was 1.4 and 1.3 respectively for maropitant, and 1.8 and 1.5 respectively for CJ-18518 (metabolite). The antiemetic activity of the CJ-18518 is limited as it has been shown to minimally cross the blood brain barrier (Study A482R-US-12-010).

7. Conclusions: The study results support an adequate safety profile for maropitant citrate when administered at 1 mg/kg by IV injection once daily for 5 consecutive days in cats.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs and cats. 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 Injectable Solution:

WARNINGS: Not for use in humans. Keep out of reach of children. In case of accidental injection or exposure, seek medical advice. Topical exposure may elicit localized allergic skin reactions in some individuals. Repeated or prolonged exposure may lead to skin sensitization. In case of accidental skin exposure, wash with soap and water. CERENIA Injectable Solution 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 Injectable Solution, when used according to the label, is safe and effective for the prevention and treatment of acute vomiting in dogs, and for the treatment of vomiting in cats.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Professional expertise in needed to diagnose and treat vomiting in dogs and cats.

B. Exclusivity

This supplemental approval for CERENIA Injectable Solution 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 and effectiveness studies. This exclusivity begins as of the date our approval letter and only applies to intravenous administration in dogs and cats, and administration 45-60 minutes prior to use of emetogenic medications in dogs.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or 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.