

Date of Approval: May 16, 2012

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-263

CERENIA

(maropitant citrate)
Injectable Solution
Cats

To add the indication "for the treatment of vomiting in cats"

Sponsored by:

Pfizer, Inc.

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I. GENERAL INFORMATION:

- A. File Number:** NADA 141-263
- B. Sponsor:** Pfizer, Inc.,
235 East 42d St.
New York, NY 10017

Drug Labeler Code: 000069
- C. Proprietary Name:** CERENIA Injectable Solution
- 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. How Dispensed:** Rx
- J. Dosage:** Administer CERENIA Injectable Solution subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 1 mL/10 kg (1 mL/22 lb) of body weight once daily for up to 5 consecutive days.
- K. Route of Administration:** Subcutaneous injection
- L. Species/Class:** Cats
- M. Indications:** For the prevention and treatment of acute vomiting in dogs and for the treatment of vomiting in cats.
- N. Effect of Supplement:** To add the indication "for the treatment of vomiting in cats."

II. EFFECTIVENESS:

A. Dosage Characterization:

A dose of 1 mg/kg of CERENIA Injectable solution administered subcutaneously was selected for the treatment of acute vomiting in cats based upon the following studies:

1. Dose Selection (Study 1981C-60-08-335):

Forty cats, eight per treatment group, were administered CERENIA Injectable Solution subcutaneously at dosages of 0.0, 0.1, 0.5, 1.0, or 2.0 mg/kg body weight one hour prior to administration of an emetogen, xylazine. Immediately after xylazine administration, cats were observed continuously for one hour and the number of emetic events was recorded. The primary effectiveness variable, number of emetic events, was analyzed using a general linear model and least squares (LS) mean contrasts.

CERENIA administered at dosages of 0.5, 1.0, or 2.0 mg/kg body weight reduced emesis to <0.2 LS mean emetic events per cat compared to >2.4 LS mean emetic events per cat administered 0.1 and 0.0 mg/kg.

Treatment with CERENIA was associated with moderate to marked response to injection (characterized by vocalizing, retreating and/or hissing), injection site swelling, and hypersalivation.

2. Dose Confirmation (Study 1981C-60-08-336):

Thirty-six cats, twelve per treatment group, were administered CERENIA Injectable Solution at dosages of 0.0, 0.5, or 1.0 mg/kg body weight 23 hours prior to the administration of an emetogen, xylazine. Immediately after xylazine administration, cats were observed continuously for one hour and the number of emetic events was recorded.

Twelve of 12 cats administered a dosage of 0 mg/kg exhibited vomiting during the one hour observation following xylazine administration, with a range of 1 to 3 emetic events. Of CERENIA-treated cats, seven of 12 cats that were administered a dosage of 0.5 mg/kg and 4 of 12 administered a dosage of 1.0 mg/kg exhibited vomiting during the one hour observation following xylazine administration.

Treatment with CERENIA was associated with moderate to marked response to injection (characterized by vocalizing, retreating and/or hissing) and hypersalivation in one cat.

B. Substantial Evidence:

Study Title and Number: Efficacy and safety of CERENIA Injectable Solution for the treatment of vomiting in cats presented as veterinary patients. Study # 1982C-60-09-347.

Type of Study: Field effectiveness study

Study Dates: August 27, 2009 – September 2, 2010

Locations and Investigators:

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General Design:

1. Purpose of Study: To demonstrate the effectiveness of CERENIA Injectable Solution when administered subcutaneously once daily for up to five consecutive days at a dosage of 1.0 mg/kg, for the treatment of vomiting in cats presented as veterinary patients. Also, to demonstrate the safety of CERENIA Injectable Solution when administered to cats under field conditions.
2. Description of Test Animals: One hundred ninety-five cats were enrolled in the study (133 CERENIA-treated and 62 placebo-treated) of various breeds (predominately domestic short hairs) weighing from 4.0 – 19.7 pounds at enrollment. Cats diagnosed with gastritis and gastroenteritis accounted for 105 of the total enrolled cats (53.8%). Other common diagnoses included pancreatitis and pancreatitis combinations (17 cats), inflammatory bowel disease (14), neoplasia (7), hepatic lipidosis (7), constipation (5), and chronic renal failure (5). Cats ranged in age from 0.4 – 19.0 years of age; 49.2% were spayed females and 47.2% were neutered males. One hundred sixty-five (111 CERENIA-treated and 54 placebo-treated) cats were included in the per protocol set for analysis of effectiveness.
3. Control and Treatment Groups:

Table 1: Control and Treatment Groups

Treatment Group	Dosage Form	Regimen	Route	Number of Cats
T01	0.0 mg/kg	Once daily for up to 5 consecutive days ¹	SC	62 cats
Placebo (Saline)	0.1 mL/kg			(31 M, 31 F)
T02	1.0 mg/kg	Once daily for up to 5 consecutive days ¹	SC	133 cats
CERENIA	0.1 mL/kg			(63 M, 70 F)

¹ If required, in the examining veterinarian's opinion.

4. Randomization: Within site, cats selected for the study were randomly allocated to treatment based on order of enrollment. At each site within each consecutive triplet, one cat was randomized to treatment group T01 (placebo) and 2 cats were randomized to treatment group T02 (CERENIA Injectable Solution).
5. Masking: All study participants with the exception of the Treatment Administrator were unaware of a cat's treatment allocation.
6. Inclusion Criteria:
 - Presented to a veterinary hospital with a history of recent emesis for which use of an antiemetic was warranted.
 - 16 weeks of age or older; 2.0 – 10.0 kg body weight
 - Owner provided consent for their cat to participate including hospitalization for at least the first day of the study.

7. Exclusion Criteria: Cats were excluded from the study if:
- any drugs with antiemetic properties (metoclopramide, prochlorperazine, chlorpromazine, acepromazine, aminopentamide sulfate, butorphanol, 5HT₃ antagonists, and antihistamine H1 receptor antagonists) had been administered within 72 hours of study enrollment or would need to be used concurrently during the study
 - a high degree of suspicion of gastrointestinal obstruction or toxin ingestion existed
 - the cat was severely compromised and not expected to survive the study period
 - the cat was pregnant, lactating, or used for breeding
 - the cat had been enrolled in the study previously
8. Drug Administration:
- a. Dosage amount, frequency, and duration: Administration was limited to a single dose within each 24-hour period for up to five consecutive days as determined by a Study Veterinarian. Treatment doses were calculated according to the recorded Day 0 body weight at a dosage of 1.0 mg/kg body weight. Equivalent volumes of saline were administered to cats allocated to receive placebo treatment.

Table 2: Numbers of Cats Administered 1-5 Doses

Total # of doses administered	Placebo (T01) n=54 cats ¹	CERENIA (T02) n=111 cats ¹
1	34.0 (63.0%)	77.0 (69.4%)
2	11.0 (20.4%)	25.0 (22.5%)
3	4.0 (7.4%)	4.0 (3.6%)
4	2.0 (3.7%)	4.0 (3.6%)
5	3.0 (5.6%)	1.0 (0.9%)

¹ Per protocol set

- b. Route of administration: subcutaneous injection
- c. Relationship to feeding: Not specified – could be either fed or fasted.
9. Variables Measured: Clinical pathology, evidence of vomiting, injection response, injection site reaction, and general health were evaluated.
- a. Clinical Pathology: Clinical pathology samples were collected prior to administration of CERENIA or placebo on Day 0, and repeated at study completion.
- b. Evidence of Vomiting: Evidence of vomiting was recorded at four specific times after treatment administration (1 hour, 3-6 hours, 9-21 hours, and 24 hours) on study Day 0. Thereafter, evidence of vomiting was recorded twice in each 24-hour period. Evidence of vomiting was defined as vomitus observed in the cage or direct observation of a cat vomiting.

- c. Injection Response: Each cat's response to subcutaneous injection was evaluated on a scale from 0-3:
 - 0 = no response;
 - 1 = mild response (the cat was aware of the injection but did not protest);
 - 2 = moderate response (the cat objected to the injection by retreating or vocalizing);
 - 3 = significant response (the cat objected to the injection by retreating, hissing, scratching, and vocalization)
- d. Injection Site Reaction: The site of each injection was evaluated by a Study Veterinarian for pain, swelling, redness, discharge, or hair loss at 24 hours post injection. Any reaction observed was followed until resolution or for up to 14 days.
- e. General Health: Any sign of abnormal health (other than nausea or vomiting) observed at any time during the study was recorded and followed until resolution or up to 14 days post treatment.

10. Statistical Analysis: The primary effectiveness variable for treatment success was defined as the absence of vomiting during the period from the first treatment administration to the assessment of vomiting conducted at 24 hours (\pm 2 hours). The binary response of treatment success/failure was analyzed using a generalized linear mixed model with logit link and binomial error distribution. The model included the fixed effect of treatment and the random effects of clinic and clinic by treatment interaction. The back-transformed least squares mean proportion of treatment failure (with evidence of an emetic event) and 95% confidence interval was presented by treatment. If T02 (CERENIA Injectable Solution) was found to be significantly different from T01 (Placebo Control) at the two-sided 0.05 significance level for the primary effectiveness variable of treatment success and showed an increase proportion of cats successfully treated, then it was considered that the study met the criteria for substantial evidence of effectiveness.

Results:

- 1. Evidence of Vomiting: Of 165 cats included in the statistical analysis of effectiveness, 10 placebo-treated cats vomited a combined total of 15 times while two CERENIA-treated cats vomited one time each in the first 24 hours post treatment.

Table 3: Number of Emetic Events¹ and Number and Percent of Cats with Emetic Events by Treatment Group and Time Interval

Observation Interval	Number of emetic events (n)		Number and percent of cats with emetic events n (%)	
	Placebo (T01)	CERENIA (T02)	Placebo (T01) n=54 ²	CERENIA (T02) n=111 ²
1 hour ± 20 minutes post treatment	2	0	2 ³ (3.7%)	0 (0.0%)
3 - 6 hours post treatment	2	0		
9-21 hours post treatment	5	0		
24 hours ±2 hours post treatment	2	1	9 (16.7%)	2 (1.8%)
Additional observations of emetic events ⁴	4	1		
Total	15	2	10	2

¹ An emetic event is defined as observation of the act of vomiting or the presence of vomitus.

² Per protocol set

³ One cat with an emetic event in the first hour after treatment also had an emetic event in the period from 3 hours to 24 hours after treatment.

⁴ An additional observation was recorded if the cat was observed in the act of vomiting or vomitus was observed but the presence or absence of vomiting was already recorded during the observation interval.

The difference in proportion of treatment success between treatment groups was statistically significant (p = 0.0102). The percentage of animals successfully treated for vomiting with placebo was 81.5% and CERENIA was 98.2%.

2. For cats continuing antiemetic treatment, 20.0% of the placebo-treated cats (4 of 20) and 2.9% of CERENIA-treated cats (1 of 34) vomited during the second 24 hour period.

Table 4: Number of Emetic Events¹ by Treatment Group and Study Day

Treatment group	Study Day	Number of cats treated ²	Number (%) of cats with emetic event
Placebo (T01)	0	54	10 (18.5)
	1	20	4 (20.0)
	2	9	2 (22.2)
	3	5	0 (0.0)
	4	3	0 (0.0)
CERENIA Injectable Solution (T02)	0	111	2 (1.8)
	1	34	1 (2.9)
	2	9	0 (0.0)
	3	5	0 (0.0)
	4	1	0 (0.0)

¹ An emetic event is defined as observation of the act of vomiting or the presence of vomitus.

² Per Protocol set

3. Injection Response: Injections elicited no response or mild response in 96.8% (60/62) of placebo-treated cats as compared to 66.1% (88/133) CERENIA-treated cats. A moderate response was elicited in 1.6% (1/62) placebo-treated cats compared to 22.6% (30/133) of CERENIA-treated cats. A significant response was elicited in 1.6% (1/62) placebo-treated cats compared to 11.3% (15/133) CERENIA-treated cats.

Table 5: Number and Percentage of Cats with Injection Responses by Treatment Group

Response Criteria	Placebo (T01) n=62 ¹	CERENIA Injectable Solution (T02) n=133 ²
No response	53 (85.5%)	55 (41.3%)
Mild response- Cat is aware of the injection but does not protest	7 (11.3%)	33 (24.8%)
Moderate response- Cat objected to the injection by retreating or vocalizing	1 (1.6%)	30 (22.6%)
Significant response- Cat objected to the injection by retreating, hissing, scratching, and vocalizing	1 (1.6%)	15 (11.3%)

¹The 62 placebo-treated cats received a total of 102 injections during the conduct of the study; only the most severe response per cat is included here.

²The 133 CERENIA-treated cats received a total of 191 injections during the conduct of the study; only the most severe response per cat is included here.

4. Injection Site Reaction: Of 288 injection sites evaluated 24 hours after administration, one placebo-treated cat demonstrated swelling at the site of injection that resolved the following day. There were no injection site reactions observed in any cat 24 hours after administration of CERENIA Injectable Solution.
5. Concomitant Medications: Over 100 different concomitant medications were administered to cats while enrolled in the study or were prescribed at study withdrawal or completion. The most commonly used concomitant medications were replacement fluid and electrolyte solutions, antimicrobials, laxatives, and appetite stimulants.
6. Clinical Pathology:
 - a. Hematology: No treatment related effects were seen.
 - b. Serum Chemistry: No treatment related effects were seen.
7. Adverse Reactions: The following adverse reactions were reported during the course of the field study. All other clinical signs were considered unrelated to treatment.

Table 6: Frequency of Adverse Reactions

Adverse Reaction	Placebo (n=62)		CERENIA (n=133)	
	# cats	% occur.	# cats	% occur.
Moderate Response to Injection ^{1,2}	1	1.6	30	22.6
Significant Response to Injection ^{1,3}	1	1.6	15	11.3
Fever/Pyrexia	2	3.2	2	1.5
Dehydration	0	0.0	3	2.3
Lethargy	0	0.0	2	1.5
Anorexia	0	0.0	1	0.8
Hematuria	0	0.0	1	0.8
Ptyalism	0	0.0	1	0.8
Injection site swelling	1	1.6	0	0.0

¹ The clinician observed and graded each cat's response to injection.

² Cat objected to the injection by retreating and vocalizing

³ Cat objected to the injection by retreating, hissing, scratching, and vocalization

Conclusion:

CERENIA Injectable Solution (maropitant citrate) was safe and effective when administered subcutaneously at a dosage of 1.0 mg/kg body weight for up to 5 consecutive days for treatment of vomiting in cats.

III. TARGET ANIMAL SAFETY:

Study Title and Number: Margin of Safety of CERENIA Injectable Solution in Cats. Study No. 1482N-60-08-331.

Type of Study: Laboratory Study conducted under GLPs

Study Dates: April 29, 2009 to May 13, 2009

Investigator and Location: Matthew J. Krautmann, DVM, PhD, Kalamazoo, MI

General Design:

1. Purpose: To evaluate the safety of CERENIA when administered to cats subcutaneously once daily for 15 days at 0, 1, 3, and 5 mg/kg.
2. Study Design: Sixteen male and 16 female cats were randomly assigned to 1 of 4 Groups consisting of 8 cats each, and received treatment as described in Table 7. Persons who made subjective study observations and the veterinarian performing clinical observations did not know the allocation of cats to treatment groups.

Table 7: Treatment Groups

Group	Dose (mg/kg)	Frequency	Duration
1 (0X)	0 ¹	Once daily	Days 0 – 5
1 (0X)	0 ²	Once daily	Days 6 – 14
2 (1X)	1	Once daily	Days 0 – 14
3 (3X)	3	Once daily	Days 0 – 14
4 (5X)	5	Once daily	Days 0 – 14

¹1X equivalent of saline

²5X equivalent of saline

3. Animals: Purpose-bred domestic short hair cats approximately 16 weeks of age.
4. Dosing: The cats were dosed by subcutaneous injection once daily for 15 days. Both CERENIA and the control article (saline) were stored in the refrigerator and placed in a water bath set at 4° C prior to dosing. Injection sites, except for the Day 3 site, were clipped and marked immediately after administration of CERENIA or the control article by locating the injection site bleb and marking the overlying skin with an indelible marker. The Day 3 injection site was left unclipped. The injections were given in separate sites on the dorsum, or on the left or right side of the cat.
5. Variables Measured: Examination of the Day 0 injection sites was conducted by a veterinarian approximately 1, 4, and 12 hours post-treatment. Behavioral response to injection administration and method of restraint used during injections were assessed throughout the study as shown below in Tables 8 and 9. Beginning on Day 1, clinical observations and all injection sites were examined by a veterinarian twice daily prior to treatment and again at the end of the normal workday. Physical examinations were conducted on study Days -1, 7, and 14. Ophthalmic examinations were performed by a board certified veterinary ophthalmologist 9 days prior to study initiation and on Day 13. Body weight was measured pre-study and on Days 7 and 14. Food consumption was recorded throughout the study. Hematology, clinical chemistry, and urinalysis were evaluated pre-study, and Days 7 and 14. Pharmacokinetic samples were taken pre-dose on Days 1, 7, and 14, and 2, 8, and 24 hours post-dose on Day 14. At necropsy, each cat was subjected to a complete gross examination. A complete set of tissues, including bone marrow cytology specimens, was collected for histopathology evaluations. Selected organs were weighed. Histopathology evaluation included each injection site on all cats. Organ weights were recorded and histopathologic evaluations performed.

Table 8: Assessment of Behavioral Response

Assessment	Behavior
Normal	Cat was aware of the injection and did not protest
Moderate	Cat vocalized or winced but there was quick resolution
Marked	Cat scratched, bit, had marked vocalization or had a persistent response at/toward the injection site

Table 9: Assessment of Method of Restraint

Assessment	Method of Restraint
Normal	Expected restraint during a subcutaneous injection
Moderate	Increased manual restraint or cat-bag required
Protective	Substantially increased manual restraint, cat-bag, safety equipment, or additional time required

6. Statistical Methods: In all analyses, the experimental unit was the individual animal. Variables measured once (organ weights) were analyzed for treatment effects by using a mixed linear model. For variables measured more than once (body weight, feed consumption, hematology, serum chemistry, coagulation, and urine), data were examined by using a linear mixed model for repeated measures. Fixed effects included treatment, sex, day, treatment*sex, treatment*day, sex*day, and treatment *sex*day. Block-within-sex was included as a random effect and the individual animal was the subject of repeated measures and/or a random effect. When a pre-treatment value was available, it was used as a covariate in the analysis. Fixed effects were evaluated as follows, the sex-by-treatment-by-day interactions were evaluated at $\alpha = 0.05$ and the treatment main effect and all other interactions with treatment were evaluated at $\alpha = 0.10$. When there was a significant treatment effect, follow-up pair-wise comparisons were made between Group 1 and each CERENIA treatment group by using linear contrasts with a significance level of 0.1.

Results:

1. Behavioral Responses: There was dose dependent pain associated with subcutaneous administration of CERENIA. Behavioral responses were recorded as shown in Table 10.

Table 10: Animal's Response to Drug Administration

Behavioral Response	Group 1		Group 2		Group 3		Group 4	
	No. ¹	%	No. ¹	%	No. ¹	%	No. ¹	%
Normal	113	94.2	76	63.3	35	29.2	33	27.5
Moderate	7	5.8	37	30.8	75	62.5	69	57.5
Marked	0	0.0	7	5.8	10	8.3	18	15.0
Moderate + Marked	7	5.8	44	36.7	85	70.8	87	72.5

¹ Number of times observed out of 120 injections per group.

Other observations related to administration of CERENIA included persistent attention to the injection site (licking, scratching, attempted biting), conditioned behavioral responses (salivation, growling), urination, licking of the injection site, aggressive posturing, and vomiting.

- Method of Restraint: Additional restraint during the administration of CERENIA was dose dependent as shown in Table 11.

Table 11: Restraint During Drug Administration

Restraint	Group 1		Group 2		Group 3		Group 4	
	No. ¹	%	No. ¹	%	No. ¹	%	No. ¹	%
Normal	113	94.2	61	50.8	35	29.2	29	24.2
Moderate	5	4.2	56	46.7	82	68.3	84	70.0
Protective	2	1.7	3	2.5	3	2.5	7	5.8
Moderate + Protective	7	5.8	59	49.2	85	70.8	91	75.8

¹ Number of times observed out of 120 injections per group.

- Injection Site Evaluation: There was a dose dependent increase in injection site pain, heat, and redness in the multiple injection sites, associated with the administration of CERENIA. One cat each in Groups 2 and 4 experienced slight injection site pain lasting less than 2 days. Injection site heat occurred in 1 Group 3 cat for 2 days. Injection site redness ≤ 5 mm in diameter occurred in 1 cat each in Groups 1, 3, and 4 once during the study. Injection site redness ≥ 5 mm in diameter occurred in 1 Group 4 cat lasting 3 consecutive days during the study. Injection site firmness was also dose dependent. There were 2 observations of firmness ≤ 10 mm in diameter in Group 1, 39 in Group 2, 96 in Group 3, and 128 in Group 4. There were no observations of firmness > 10 mm in diameter in the Group 1 injection sites. There was one observation of firmness > 10 mm in diameter in Group 2, 15 in Group 3, and 30 in Group 4.
- Body Weight and Food Consumption: Body weight was not affected by treatment. Average daily calorie consumption in Group 4 was slightly (~ 7 g/day) lower but statistically significantly different ($p = 0.0171$) compared to Group 1.
- Clinical Observations: There were more instances of vomiting in Group 1 (6) versus vomiting in Groups 2, 3, and 4 (1). Clinical signs consistent with mild dehydration noted as dry mucous membranes occurred in all groups, with the majority occurring in Group 3. Dry mucous membranes in conjunction with

increased skin turgor were noted in Groups 3 and 4, and on the last 3 days of the study, 1 cat in Group 4 was lethargic.

6. Respiratory and Heart Rates: There were no clinically significant changes in heart rate during the study. In Groups 2, 3, and 4, respiratory rates increased to more than 80 breaths per minute on study days 7 and 14 in some cats.
7. Ophthalmic Exams: There were no clinically relevant changes related to the administration of CERENIA.
8. Clinical Pathology: There were no clinically significant changes in hematology, blood chemistry, or urinalysis during the study. One cat in Group 3 had an elevated APTT of 76.2 seconds (reference range 14-68) on Day 14 of the study. This cat's APTT results on Days -2 and 7 of the study were 42.8 and 45.3 seconds, respectively.
9. Gross Pathology and Histopathological Findings: There were no treatment related gross findings at necropsy. A total of 56 injection sites per treatment group were evaluated at necropsy.

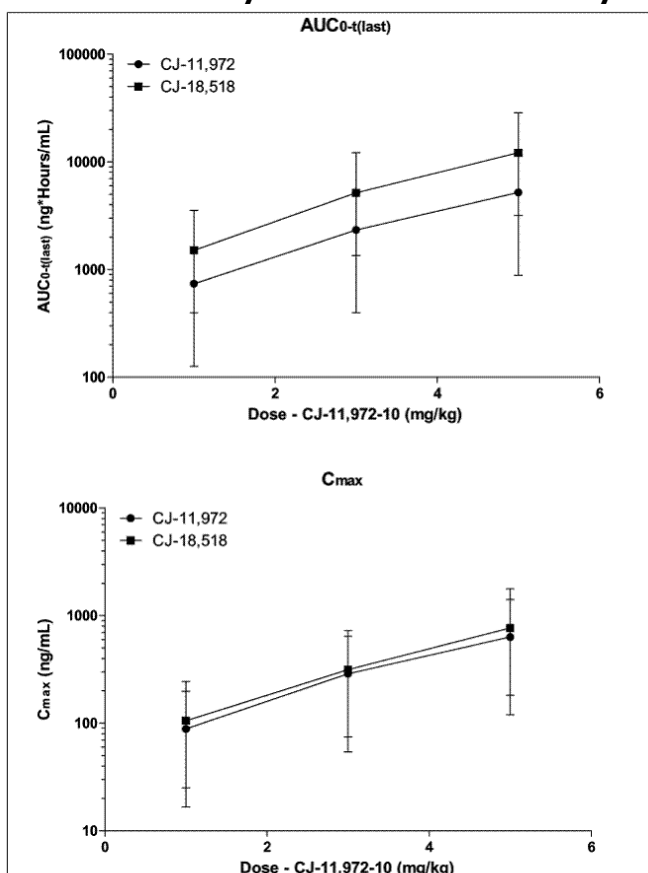
The histopathologic evaluation of Group 1 showed minimal tissue reaction at the injection sites. Where a reaction was observed for the saline injected sites on Days 9 to 14 (within 5 days of necropsy), minimal degeneration/regeneration of panniculus muscle, minimal to mild fibrosis, and minimal granulomatous mixed cell and/or neutrophilic inflammation was noted. Where a reaction was observed for Days 0 to 8 only minimal to mild fibrosis and minimal mononuclear cell infiltration were noted.

Evaluation of injection sites from CERENIA administration on Days 9-11 and 12-14 (within 5 days of necropsy) showed acute changes consisting of collagen degeneration, degeneration/regeneration of panniculus muscle, edema, fibrosis, hemorrhage, mixed cell inflammation, neutrophilic inflammation, and granulomatous inflammation. Incidence and severity were dose proportional, with severity grades generally ranging from minimal to mild or moderate in 1X and from minimal to moderate or marked in 5X. Evaluation of injection sites from CERENIA administered mid-study (Days 4-8) showed no edema, but included collagen degeneration, fibrosis, granulomatous inflammation, hemorrhage, mineral deposition, panniculus muscle degeneration/regeneration, and mononuclear cell infiltration. Lesions were present with dose proportionality but at lesser incidence and severity compared to injection sites of more recent injections. Evaluation of injection sites from CERENIA administered early in the study on Days 0-3 (approximately 2 weeks from necropsy) were characterized by collagen degeneration, fibrosis, granulomatous inflammation, edema, cavity formation, hemorrhage, panniculus muscle degeneration/regeneration, neutrophilic inflammation, and mononuclear cell infiltration, with dose proportional incidence and severity. Lesions generally were minimal to mild or moderate, except that collagen degeneration and fibrosis were more marked in some 5X cats compared to injection sites of more recent injections.

Overall, histopathologic evaluation of the injection sites showed there was an early dose dependent acute inflammatory response (neutrophilic and mixed cell inflammation, collagen degeneration, and edema) that was replaced by increased fibrosis and decreasing granulomatous inflammation.

Pharmacokinetics: Concentrations of the parent compound, CERENIA, and its major metabolite, CJ-18,518, were quantified during the study. Drug concentrations were found to be proportional following a subcutaneous injection of 1 mg/kg or 3 mg/kg, and concentrations of the parent compound and its active metabolite were slightly greater than dose proportional after a daily subcutaneous injection of 5 mg/kg. The steady state area under the concentration-time curve ($AUC_{0-\tau}$) and the peak concentrations of the parent compound and its metabolite are provided in Figure 1.

Figure 1. Mean (90% CI) Plasma $AUC_{0-t(\text{last})}$ and C_{max} of CJ-11,972 and CJ-18,518 on Day 14 in Cats Receiving 1, 3, or 5 mg/kg/day Maropitant Citrate (CJ-11,972-10) Subcutaneously for 15 Consecutive Days



Conclusion:

The subcutaneous administration of CERENIA at 1, 3, and 5 mg/kg in 16-week-old cats results in injection pain and results in the need for increased restraint during injections. CERENIA also causes injection site reactions (pain, heat, redness, firmness) and inflammatory histological changes at the injection site.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, which are non-food animals. 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 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 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 and 21 CFR Part 514. The data demonstrate that CERENIA Injectable Solution, when used according to the label, is safe and effective for the treatment of vomiting in cats.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and treat vomiting in cats.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

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