Date of Approval: May 16, 2012

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-263

CERENIA

(maropitant citrate)
Injectable Solution
Dogs

To decrease the minimum age to "for use in dogs 8 weeks and older" for the prevention and treatment of acute vomiting in dogs

Sponsored by:

Pfizer, Inc.

TABLE OF CONTENTS

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 (SC) 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:	Dogs
M. Indications:	For the prevention and treatment of acute vomiting in dogs.
N. Effect of Supplement:	To decrease the minimum age to "for use in dogs 8 weeks and older" for the prevention and treatment of acute vomiting in dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage/dosage range. The Freedom of Information (FOI) Summary for the original approval of NADA 141-263, dated January 29, 2007, contains dosage characterization information for dogs.

B. Substantial Evidence of Effectiveness:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-263, dated January 29, 2007, contains a summary of studies that demonstrate effectiveness of the drug for dogs.

III. TARGET ANIMAL SAFETY

The FOI Summary for the original CERENIA approval (see Freedom Of Information Summary Original New Animal Drug Application NADA 141-263 dated January 29, 2007) contains a summary of target animal safety studies for dogs 8 and 16 weeks of age. CERENIA's general clinical effects are on food consumption, hydration status, and body weight and these were noted in both age groups (8 and 16 week old pups). The original 8 week old dog study data did not support the safe use of CERENIA because of confounding conditions related to illness, post-weaning effects, minimal acclimation period, and the occurrence of dose-related bone marrow hypocellularity (BMH) that was not seen in dogs >16 weeks of age. An increased incidence of treatment-related BMH was seen at 24 mg/kg (3 times the dose for prevention of vomiting due to motion sickness) suggesting that this effect could be dose related.

For this supplement, a Target Animal Safety (TAS) study was conducted in 10 week old dogs. The reason for conducting the study was to eliminate the confounding effects noted in the preapproval 8 week old dog TAS studies and evaluate the safe use of maropitant for dogs <16 weeks of age.

Study Title and Number: Use of CERENIA in 10 Week Old Dogs (#1467R-60-08-853).

1. Type of Study: Laboratory Safety Study not conducted per GLPs

2. Study Dates: April 1 to April 30, 2008

3. Investigator and Location:
   Heather R. Francis, BS, LAT
   Pfizer Animal Health
   Richland, MI 49083

4. General Design

a. Purpose of Study: The objective of this study was to characterize the clinical, clinical pathology, and pathology effects of the label dosage of CERENIA (maropitant citrate) in healthy dogs approximately 10 weeks of age.

b. Description of Test Animals: Twenty male and 20 female Beagle dogs were used in this study. The ages of the dogs at arrival were 40-44 days (approximately 6 weeks). All dogs were 64-70 days old on day 0 (approximately 10 weeks).

c. Control and Treatment Groups:

Table 1: Control and Treatment Groups

Phase	Treatment Group	Number of Animals	Formulation/ Dose	Route	Tx Days	Necropsy Day
Phase 1	T01 Placebo Tablet	4 males, 4 females	Placebo Tablets	Oral	0, 1	Day 2
Phase 1	T02 CERENIA Tablet Motion Sickness Dose	4 males, 4 females	CERENIA 8 mg/kg	Oral	0, 1	Day 2
Phase 2	T03 Placebo Saline Injectable	4 males, 4 females	Placebo (saline solution)	SC	0 to 4	Day 5
Phase 2	T04 CERENIA Acute Injectable	4 males, 4 females	CERENIA 1 mg/kg	SC	0 to 4	Day 5
Phase 2	T05 CERENIA Tablet Acute Oral Dose	4 males, 4 females	CERENIA 2 mg/kg	Oral	0 to 4	Day 5

d. Masking: Clinical observations were conducted by persons who did not know the treatment allocation. The treatment allocation and any information that might have disclosed the treatment allocation were kept separated and concealed from those responsible for observations. The persons dosing the animals, collecting samples, and measuring body and feed weights were not masked. The pathologist was masked during gross necropsy but not masked when reading histopathology results.

e. Inclusion Criteria/Exclusion Criteria: Satisfactory physical examination, clinical pathology values, and general health observations.

f. Dose Administration: The Day -2 body weight was used to calculate the daily dose for all dogs. The motion sickness label dose (8 mg/kg) was used for each dog in T02 and the acute emesis label dosages were used for T04 (injectable dose, 1 mg/kg) and T05 (oral dose, 2 mg/kg). The oral placebo dose (T01) was 1/4 tablet per dog per day. The saline placebo dose (T03) was volume equivalent to the corresponding label dose (0.1 mL/kg) of CERENIA Injectable Solution. All dogs were dosed once daily on days 0 and 1 for all treatments. Dogs in T03, T04, and T05 continued to be dosed once daily on days 2, 3, and 4.

g. Variables Measured: Health status was evaluated using data collected in physical examinations, general health observations (including injection site), food consumption, and body weight. Samples were collected to assess clinical pathology values (serum chemistry panel, hematology, coagulation values, and urinalysis) and plasma maropitant citrate blood levels. At necropsy, gross and histopathology findings (including bone marrow histopathology) were evaluated.

h. Statistical Methods: Summary statistics were used to evaluate the variables. No statistical analysis was performed.

5. Results:

a. Clinical findings: The main treatment related finding in the study was a decrease in food consumption in males that received maropitant at 8 mg/kg for 2 days compared to control dogs. Flinching and shaking/scratching were more frequent and persistent in maropitant injected dogs compared to the corresponding control dogs. The reactions were mild and there was no other indication of injection site pathology. Dogs in all treatment groups (including controls) experienced transient diarrhea (some with hematochezia).

b. Clinical pathology: There was a slight post-treatment increase in hematocrit and hemoglobin and a decrease in percent reticulocytes in T02 males (results reflect mean values). The post-treatment red blood cell (RBC) counts were also numerically higher in T02 compared to T01. During phase 2, the control group (T03) had higher hematocrit, hemoglobin, and RBC values than the T04 (CERENIA Injectable) and higher RBC counts than T05 (oral high dose CERENIA Tablet). There was also an increase in fibrinogen in T02 and T04 compared to their controls that was not seen in T05. Minor changes in other clinical pathology variables occurred including variations in lymphocyte counts, alanine aminotransferase (ALT), amylase, activated partial prothrombin time (APTT), aspartate aminotransferase (AST), alkaline phosphatase (AP), blood urea nitrogen (BUN), chloride (CL), creatine kinase (CK), triglycerides (TRIG), mean cell hemoglobin concentration (MCHC), and urine pH.

In T02 (8 mg/kg oral CERENIA Tablet), 2 dogs had individual values below the reference range for reticulocyte counts. Unlike other dogs in T02, these 2 dogs did not have elevated hematocrit and hemoglobin values. All other hematology values outside the reference ranges in dogs in T02 were not clinically significant. A single dog in T04 had hypocellularity of the femoral bone marrow (see Pathology below); measurements of reticulocytes were not available for this dog. However, 4 of 8 dogs in the phase 2 placebo group (T03) showed decreases in percent reticulocytes.

c. Pathology: Although histology was done on bone marrow from each dog's sternum, no sternum bone marrow smears were examined for cellularity. One male dog in T04 (1 mg/kg CERENIA Injectable) had hypocellular femoral bone marrow. The pathologist described the finding as minimal (scored 1 of possible 4). Some areas of inflammation were noted in the kidneys, lungs, and cervical and mediastinal lymph nodes of this dog. However, many other dogs had similar inflammatory findings in various organs. This dog had normal values for all clinical pathology variables, except for neutrophils (below normal range), monocytes, and triglycerides (above normal range) on day 5; however, no values were available for reticulocytes. Pathology findings did not correlate with any clinical abnormalities.

d. Pharmacokinetics: Compared to prior pharmacokinetic data generated in adult Beagle dogs (16 weeks of age), 10 week old dogs in this study that received either a 1 mg/kg CERENIA Injectable or 2 mg/kg CERENIA Tablet dose showed lower than expected drug exposure. The reasons for this lower than anticipated exposure could not be determined. In contrast, exposure following an 8 mg/kg oral dose was comparable to that observed in adult Beagle dogs.

6. Conclusions: Maropitant was well tolerated in healthy puppies 10 weeks of age. The main treatment related findings were mild pain associated with injection and a decrease in food consumption in males orally administered maropitant at 8 mg/kg for 2 days. Hypocellular bone marrow was observed in 1 dog administered 1 mg/kg CERENIA Injectable; the clinical significance of this finding remains undetermined.

In studies used for the original CERENIA approval in dogs (see Freedom Of Information Summary Original New Animal Drug Application 141-263 dated January 29, 2007) there are indications that adverse effects (including bone marrow hypocellularity) are dose related. Therefore, the minimum recommended age limit for the prevention of acute vomiting is changed to 8 weeks. However, because the dose is higher (8 mg/kg instead of 1-2 mg/kg), the minimal recommended age limit for the prevention of motion sickness will remain at 16 weeks.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, 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 prevention and treatment of acute vomiting in dogs.

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 dogs.

B. Exclusivity:

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

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.