Date of Approval: January 29, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-263

CERENIA

(maropitant citrate)
Injectable Solution
Dogs

For the prevention and treatment of acute vomiting in dogs.

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(s):	CERENIA Injectable Solution
D. Established Name(s):	Maropitant citrate
E. Pharmacological Category:	Antiemetic
F. Dosage Form(s):	Injectable Solution
G. Amount of Active Ingredient(s):	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(s):	Administer CERENIA Injectable Solution subcutaneously at 1.0 mg/kg (0.45 mg/lb) equal to 1.0 mL/10 kg (1.0 mL/22 lb) of body weight once daily for up to 5 consecutive days.
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es):	Dogs
M. Indication(s):	For the prevention and treatment of acute vomiting in dogs.

II. EFFECTIVENESS:

The terms maropitant, maropitant citrate, CJ-11,972, and CERENIA are used interchangeably throughout this document. These terms all refer to the same drug product.

A. Dosage Characterization:

Injectable Subcutaneous Dose of 1 mg/kg:
A subcutaneous dosage of 1 mg/kg was selected as the dosage for the prevention and treatment of acute vomiting in dogs using data generated in a comparative pharmacokinetic study. Twelve Beagle dogs in a crossover design study with 6 dogs per group (3 males and 3 females) were administered either 2 mg/kg maropitant orally or 1 mg/kg maropitant subcutaneously. Blood samples were collected at 0.5, 1, 2, 3, 4, 8, 12, and 24 hours after drug administration and the plasma was analyzed to determine maropitant concentration. No statistical differences in the time to achieve maximum plasma concentration (T_{max}), in maximum concentration (C_{max}), or in area under the plasma concentration curve ($AUC_{0 \text{ to } 24}$) were detected between maropitant administered subcutaneously at a dosage of 1 mg/kg or orally at 2 mg/kg. These data demonstrate that a subcutaneous dose of 1 mg/kg maropitant provides systemic exposure comparable to that provided by a 2 mg/kg oral dosage of maropitant. The 2 mg/kg oral dosage of maropitant was selected based on the results of an oral dose titration study (#5961C-12-01-241) in which maropitant at 2 mg/kg was found to be effective. Therefore a dose of 1 mg/kg subcutaneously was chosen.

B. Substantial Evidence:

Two laboratory studies and two field studies were conducted to confirm the dose and to support substantial evidence of effectiveness for the prevention and treatment of acute vomiting in dogs.

1. Dose Confirmation, Laboratory study at a dosage of 1 mg/kg injected subcutaneously.

a) Study Title and Number: Dose confirmation of the efficacy of CJ-11,972 for syrup of ipecac (Ipecacuanha)-induced emesis in dogs. Study #1960C-60-01-587.

b) Type of Study: Laboratory dose confirmation study conducted according to VICH GL9 GCP Guidance.

c) Study Dates: June 9 - 11, 2003.

d) Location and Investigator(s):

David R. Young, DVM, PhD
Young Veterinary Research Services (YVRS), Turlock, CA

e) General Design

1) Purpose of Study: To confirm the antiemetic effectiveness of a single dose of 1 mg/kg maropitant administered to dogs by subcutaneous injection approximately 1 hour prior to administration of syrup of ipecac.

2) Description of Test Animals: 24 Beagle dogs, 12 sexually intact males and 12 sexually intact females, approximately 2 years, 5 months old to 8 years, 7 months old, weighing between 8.1 – 18.6 kg.

3) Control and Treatment Group(s):

Table 1.1 Control and Treatment Groups

Tx Group	Dosage (mg/kg)	Route of Administration	Number of Animals
T01 placebo	0	SC	12 (6M, 6F)
T02 maropitant	1	SC	12 (6M, 6F)

4) Randomization: The 24 dogs were randomly divided into three batches, each batch containing 8 dogs (4 males and 4 females). Within each batch, animals were randomly allocated to treatment and pen according to a randomized complete block design with a two way treatment structure (sex and treatment). Blocking was based on pen location and assessors (two sets of two assessors). Each block consisted of one T01 male, one T01 female, one T02 male and one T02 female and two independent assessors (one assessor performed nausea assessments and the other counted the number of emetic events for an individual animal).

5) Masking: All personnel making general health observations or clinical assessments were unaware of treatment allocation.

6) Inclusion Criteria/Exclusion Criteria: Healthy dogs.

7) Drug Administration:

a. Dosage amount, frequency, and duration: Dogs were administered 1 mg/kg maropitant or placebo (saline) on Day 0 once, approximately one hour before oral administration of syrup of ipecac. Dogs were administered syrup of ipecac at a dose of 0.5 mL/kg orally.

b. Route of administration: Subcutaneous injection in the dorsal scapular region.

8) Variables Measured: General health observations, number of emetic events and clinical assessment of nausea.

   a. General health observations: Dogs were observed twice daily from Study Day -5 through -1 and once prior to treatment on Day 0.

   b. Emetic Events: Immediately following administration of syrup of ipecac, each animal was continuously observed for one hour for emetic events (vomiting or retching). The time of each emetic event observed was recorded.

   c. Clinical assessment of nausea: Prior to treatment on Day 0, a baseline nausea assessment was performed on each dog. Immediately following administration of syrup of ipecac, each animal was observed for nausea for 30 seconds at 3-minute intervals for 1 hour. Assessments included increased salivation, lip licking, frequent and/or exaggerated swallowing motions, lethargy, restlessness, and/or panting. These were quantified using a Visual Analog Scale (VAS). The degree of nausea was quantified by drawing a single vertical line to intersect a 100 millimeter horizontal line. The distance in millimeters from this intersection to the left origin of the VAS line represented the severity of nausea. A score of zero on the VAS was defined as no nausea, and a score of 100 was defined as the worst possible nausea the animal could experience.

9) Statistical Analysis: The square root of the number of emetic events was analyzed using a linear mixed model. VAS scores for nausea were analyzed using a linear mixed model with repeated measures. Statistical differences were assessed using a two-sided 5% level of significance.

10) Criteria for Success/Failure: The primary effectiveness variable is the number of emetic events. Another effectiveness variable is the VAS score for nausea.

f) Results

1) Clinical Observations and Exams: No signs of abnormal health were observed during the study.

2) Emetic Events: All placebo-treated dogs exhibited vomiting during the one hour observation period following syrup of ipecac administration with a range of 1 to 14 emetic events. Three of the 12 maropitant-treated dogs exhibited vomiting after receiving syrup of ipecac with 1, 2 and 23 emetic events recorded per dog.

Table 1.2 Frequency Distribution of Whether or Not Dogs Exhibited Emetic Events in the One Hour After Receiving Syrup of Ipecac

Treatment	#	Number of Animals **Not**	%	Number of Animals	%

		Exhibiting Emesis		Exhibiting Emesis	
T01 placebo	12	0	0	12	100
T02 maropitant	12	9	75	3	25

The mean number of emetic events observed in the maropitant-treated dogs was significantly less (P = 0.0052) than that observed in the placebo-treated dogs.

3) VAS Scores for Nausea: Least-squares mean VAS scores for nausea following syrup of ipecac administration ranged from 5.7 to 52.2 for the placebo-treated dogs compared to a range of 6.2 to 26.2 for the maropitant-treated dogs. Although no significant differences were noted in VAS scores between treatments for the first 33 minutes after syrup of ipecac administration, from 36 to 60 minutes, maropitant-treated dogs were lower than those of placebo-treated dogs at all time points except 54 minutes.

g) Adverse Reactions: None reported.

h) Conclusion: Maropitant at a dosage of 1 mg/kg administered subcutaneously was effective in the prevention of vomiting induced by syrup of ipecac.

2. Dose Confirmation, Laboratory study at a dosage of 1 mg/kg injected subcutaneously.

a) Study Title and Number: Dose confirmation of the efficacy of CJ-11,972 for apomorphine-induced emesis in dogs. Study #1960C-60-01-588.

b) Type of Study: Dose confirmation study conducted according to VICH GL9 GCP Guidance

c) Study Dates: June 23 - 25, 2003

d) Location and Investigator:

David R. Young, DVM, PhD
Young Veterinary Research Services (YVRS), Turlock, CA

e) General Design

1) Purpose of Study: To confirm the antiemetic effectiveness of a single dose of 1 mg/kg maropitant administered to dogs by subcutaneous injection approximately 1 hour prior to administration of apomorphine.

2) Description of Test Animals: 24 Beagle dogs, 12 sexually intact males and 12 sexually intact females, approximately 2 years, 5 months old to 8 years, 7 months old, weighing between 8.3 – 19.2 kg.

3) Control and Treatment Group(s):

Table 2.1 Treatment and Control Groups

Tx Group	Dosage (mg/kg)	Route of Administration	Number of Animals
T01 placebo	0	SC	12 (6M, 6F)
T02 maropitant	1	SC	12 (6M, 6F)

4) Randomization: The 24 dogs were randomly divided into three batches, each batch containing 8 dogs (4 males and 4 females). Within each batch, animals were randomly allocated to treatment and pen according to a randomized complete block design with a two way treatment structure (sex and treatment). Blocking was based on pen location and assessors (two sets of two assessors). Each block consisted of one T01 male, one T01 female, one T02 male and one T02 female and two independent assessors (one assessor performed nausea assessments and the other counted the number of emetic events for an individual animal).

5) Masking: All personnel making general health observations or clinical assessments were unaware of treatment allocation.

6) Inclusion Criteria/Exclusion Criteria: Healthy dogs.

7) Drug Administration:

   a. Dosage amount, frequency, and duration: Dogs were administered 1 mg/kg maropitant or placebo (saline) on Day 0 once, approximately one hour before intravenous administration of apomorphine. Dogs were administered apomorphine intravenously at a dosage of 0.01 mg/kg.

   b. Route of administration: Subcutaneous injection in the dorsal scapular region.

8) Parameters Measured: General health observations, number of emetic events and clinical assessment of nausea.

   a. General health observations: Dogs were observed twice daily from Study Day -5 through -1 and once prior to treatment on Day 0. All dogs had a physical examination, including rectal temperature, thoracic auscultation, skin and hair coat, and general condition on Day -6.

b. Emetic Events: Immediately following intravenous administration of apomorphine, each animal was continuously observed for 30 minutes for emetic events (vomiting or retching). The time of each emetic event observed was recorded.

c. Clinical assessment of nausea: Prior to treatment on Day 0, a baseline nausea assessment was performed on each dog. Immediately following administration of apomorphine, each animal was observed for nausea for 30 seconds at 3-minute intervals for 30 minutes. Assessments included increased salivation, lip licking, frequent and/or exaggerated swallowing motions, lethargy, restlessness, and/or panting. These were quantified using a Visual Analog Scale (VAS). The degree of nausea was quantified by drawing a single vertical line to intersect a 100 millimeter horizontal line. The distance in millimeters from this intersection to the left origin of the VAS line represented the severity of nausea. A score of zero on the VAS was defined as no nausea, and a score of 100 was defined as the worst possible nausea the animal could experience.

9) Statistical Analysis: The square root of the number of emetic events was analyzed using a linear mixed model. VAS scores for nausea were analyzed using a linear mixed model with repeated measures. *A priori* contrasts among least squares mean VAS scores were used to assess treatment differences. Statistical differences were assessed using a two-sided 5% level of significance.

10) Criteria for Success/Failure: The primary effectiveness parameter is the number of emetic events. Another effectiveness parameter is the VAS score for nausea.

f) Results

1) Clinical Observations and Exams: No signs of abnormal health were observed during the study.

2) Emetic Events: Ten of the 12 placebo-treated dogs exhibited vomiting during the 30 minute observation period following apomorphine administration with a range of 1 to 3 emetic events. Two of the 12 maropitant-treated dogs exhibited vomiting after receiving apomorphine with 1 and 6 emetic events recorded per dog respectively.

Table 2.2 Frequency Distribution of Whether or Not Dogs Exhibited Emetic Events in the 30 Minutes After Receiving Apomorphine

Treatment	#	Number of Animals **Not** Exhibiting Emesis	%	Number of Animals Exhibiting Emesis	%
T01 placebo	12	2	16.7	10	83.3

T02 maropitant	12	10	83.3	2	16.7

The mean number of emetic events observed in the maropitant-treated dogs was significantly less (P = 0.0029) than that observed in the placebo-treated dogs.

3) VAS Scores for Nausea Least-squares mean VAS scores for nausea following apomorphine administration ranged from 5.8 to 53.8 for the placebo-treated dogs compared to a range of 1.4 to 26.3 for the maropitant-treated dogs. VAS scores for maropitant-treated dogs were significantly lower ($P \leq 0.047$) than those of placebo-treated dogs at time points from 3 to 12 minutes and then at the 27 minute time point after receiving apomorphine. No significant differences in VAS scores were found at any other time points.

g) Adverse Reactions: None reported.

h) Conclusions: Maropitant at a dose of 1 mg/kg administered subcutaneously was effective in the prevention of vomiting induced by apomorphine.

3. Clinical Field Study to evaluate the effectiveness of maropitant at a dose of 1 mg/kg subcutaneously for the prevention and treatment of acute vomiting caused by administration of cisplatin

a) Study Title and Number: Field effectiveness and safety of CJ-11,972 subcutaneously administered at 1 mg/kg (prior to or following cisplatin treatment) for the prevention and control of cisplatin-induced emesis in canine cancer patients. Study #1962C-60-02-626.

b) Type of Study: Field safety and effectiveness study.

c) Study Dates: November 14, 2003 – September 17, 2004.

d) Location(s) and Investigator(s):

Craig A. Clifford, DVM
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Seattle, WA

Joyce Obradovich, DVM
Canton, MI

Gerald Post, DVM
Westbury, NY

David M. Vail, DVM
Madison, WI

e) General Design:

1) Purpose of Study: To assess the field effectiveness and safety of saline (0.1 mL/kg) and maropitant (1 mg/kg = 0.1 mL/kg) administered as single subcutaneous dose prior to and/or after cisplatin administration for the prevention and treatment of cisplatin-induced emesis.

2) Description of Test Animals: 122 dogs (91 pure-breed and 31 mixed-breed), 59 females and 63 males, ranging from 1 to 14 years old, weighing between 8.3 and 68.0 kg. Rottweilers, Labrador Retrievers and Golden Retrievers were over represented with 16, 12, and 8 enrolled in the study respectively. The majority of dogs enrolled in the study were being treated for osteosarcoma. Of lesser frequency were transitional cell carcinoma, squamous cell carcinoma, apocrine (anal sac) adenocarcinoma, thyroid carcinoma, prostatic carcinoma, nasal carcinoma, bronchogenic carcinoma, pulmonary carcinoma and mesenchyoma.

3) Control and Treatment Group(s):

Table 3.1: Control and Treatment Groups

Tx Group	Prior to Cisplatin	Following 1st Emetic Event	Regimen	Route	Number of Animals
T01	Saline 0.1 mL/kg	Saline 0.1 mL/kg	Once prior to or after cisplatin	SC	41 (15M, 26F)
T02	Saline 0.1 mL/kg	Maropitant 1 mg/kg	Once prior to or after cisplatin	SC	42 (19M, 23F)
T03	Maropitant 1 mg/kg	Saline 0.1 mL/kg	Once prior to or after cisplatin	SC	39 (29M, 10F)

4) Randomization: Within each hospital, a randomized block design with a one-way treatment structure was used to allocate animals to treatments. Dogs were randomized to one of the three treatment groups (T01 – saline/saline, T02 – saline/maropitant, and T03 – maropitant/saline) in each block based on order of enrollment.

5) Masking: All study participants, with the exception of the Dispenser, were unaware of a dog's treatment allocation.

6) Inclusion Criteria: Patients were selected for the study from client-owned dogs present to the veterinary practice. Patients enrolled in the study satisfied the following inclusion criteria:

- Cisplatin therapy was warranted,
- Clients had to consent to hospitalize their dogs for the entire study period,
- Dogs had to be non-breeding males or non-breeding, non-pregnant females,
- Dogs had to be greater than 16 weeks of age and
- Prior to enrollment, all dogs were given a standard physical examination and were determined suitable for enrollment by the examining veterinarian.

7) Exclusion Criteria: Dogs were excluded from the study if:

- They had been treated with drugs with antiemetic properties within 24 hours of Day 0.
- They were severely compromised and not expected to survive the study period.

8) Drug Administration:

   a) Dosage amount, frequency, and duration: On Day 0, saline (0.1 mL/kg) or maropitant (0.1 mL/kg) were administered subcutaneously to each dog based on Day 0 body weight. Approximately 1 hour following treatment, cisplatin therapy (mean dose of 2.27 mg/kg, see Table 3.2) was initiated. A post-cisplatin subcutaneous injection of saline or maropitant was administered as soon as possible after the first emetic event.

Table 3.2: Cisplatin Dose (mg/kg) Administered

Treatment	# of Dogs	Mean	Median	Minimum	Maximum
T01 (Saline/Saline)	41	2.25	2.20	1.73	6.03
T02 (Saline/CJ-11,972)	42	2.23	2.13	1.88	3.37
T03 (CJ-11,972/Saline)	39	2.23	2.17	1.65	3.39
All	122	2.27	2.17	1.65	6.03

   b) Route of administration: Subcutaneous injection in the dorsal scapular region.

9) Variables Measured: Number of emetic events and injection site.

   a) Emetic Events: Following the start of intravenous therapy with cisplatin, dogs were observed continuously for vomiting/retching for five hours. Any dog that exhibited an unacceptable frequency of vomition (6 events) after post-cisplatin treatment was examined by the examining veterinarian who decided whether that dog should be removed from the study and treated with an alternative antiemetic.

   b) Injection Site Evaluation: Injection sites were observed once 24 hours following start of cisplatin administration.

   c) Abnormal Health: Dogs that failed to complete the study were withdrawn from the effectiveness portion of the study, although safety observations continued for approximately 24 hours following cisplatin therapy.

10) Statistical Analysis: The number of emetic events occurring after treatment administration was modeled using a generalized linear mixed model with a log link and Poisson error distribution. The Cochran-Mantel-Haenszel test was used to compare the number of treatment failures between the placebo and maropitant groups. Treatment failures were defined as dogs having at least 6 emetic events after vomit inducement. Statistical differences were assessed using a one-sided 5% level of significance.

11) Criteria for Success/Failure: The primary effectiveness variable was the number of emetic events.

f) Results:

1) Treatment of acute vomiting indication [T01 (saline/saline) versus T02 (saline/maropitant)]: Only dogs that exhibited vomiting in the five hours immediately following cisplatin therapy received an injection with either saline (T01) or maropitant (T02). The emetic events included in the analysis were those which occurred in the five hours following cisplatin therapy and after the post-cisplatin injection with either saline or maropitant. Significantly fewer ($P = 0.0005$) emetic events were observed in the maropitant-treated dogs than in the saline-treated dogs. There were significantly fewer ($P < 0.0001$) treatment failures in the maropitant group (2 of 38 dogs) than in the saline group (21 of 39 dogs).

2) Prevention of acute vomiting indication [T01 (saline/saline) versus T03 (maropitant/saline)]: All dogs in Groups T01 (41) and T03 (39) and all emetic events following cisplatin therapy were included in the analysis for prevention of cisplatin-induced vomiting. Thirty-seven of 39 dogs (94.9%) in Group T03 experienced no emetic events compared to 2 of 41 dogs (4.9%) in Group T01. Significantly fewer ($P < 0.0001$) emetic events were observed in the maropitant-treated dogs than the saline-treated dogs.

Table 3.3: Frequency Distribution of Number of Emetic Events Over the Five-Hour Period Immediately Following Cisplatin Therapy.
For Treatment: Number of Emetic Events Post Injection.
For Prevention: Total Number of Emetic Events.

Total Number of Emetic Events	Number of Dogs (% of Dogs)			
	Treatment of Acute Vomiting		Prevention of Acute Vomiting	
	T01 (n = 39*)	T02 (n = 38*)	T01 (n = 41)	T03 (n = 39)
0	2 (5.1)	8 (21.1)	2 (4.9)	37 (94.9)
1	3 (7.7)	7 (18.4)	2 (4.9)	1 (2.6)
2	4 (10.3)	6 (15.8)	3 (7.3)	1 (2.6)
3	3 (7.7)	6 (15.8)	4 (9.8)	0 (0)
4	4 (10.3)	4 (10.5)	3 (7.3)	0 (0)
5	2 (5.1)	5 (13.2)	4 (9.8)	0 (0)
6	14 (35.9)	1 (2.6)	1 (2.4)	0 (0)
7	2 (5.1)	1 (2.6)	12 (29.3)	0 (0)
8	2 (5.1)	0 (0)	5 (12.2)	0 (0)
9	2 (5.1)	0 (0)	2 (4.9)	0 (0)
10	0 (0)	0 (0)	2 (4.9)	0 (0)
11	1 (2.6)	0 (0)	0 (0)	0 (0)
12	NA	NA	1 (2.4)	0 (0)
$\leq$ 5 emetic events	18 (46.1)	36 (94.7)	18 (43.9)	39 (100)
$\geq$ 6 emetic events (treatment failures)	21 (53.9)	2 (5.3)	23 (56.1)	0 (0)

T01 is saline/saline, T02 is saline/maropitant and T03 is maropitant/saline.
*There were initially 41 and 42 dogs in saline/saline and saline/maropitant groups, respectively. However, if a dog did not vomit following cisplatin therapy, it did not receive a post-cisplatin treatment with either saline or maropitant, and hence it was not considered in the therapeutic evaluation. Two dogs in the saline/saline group did not vomit and were excluded from the analysis. In addition, one dog in the saline/maropitant group was excluded from effectiveness analysis due to overdosing.

3) Injection Site Evaluation: Two dogs treated with maropitant displayed signs of pain or vocalized during injection. One dog that received an injection of maropitant had an injection site swelling. No abnormal reactions were recorded for dogs receiving saline injections.

4) Concomitant Medications: Dogs participating in this study also received: antibiotics, NSAIDs, cyclosporine, pain medications, joint supplements, antacids, sucralfate, ACE inhibitors, phenobarbital, steroids, and thyroxine.

g. Adverse Reactions: The following adverse reactions were reported during the conduct of the study.

Table 3.4: Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n = 41)		Maropitant (n = 81)	
	# dogs	% occur	# dogs	% occur
Diarrhea	1	2.4	6	7.4
Anorexia	1	2.4	3	3.7
Lethargy	0	0	2	2.5
Pain upon injection	0	0	2	2.5
Injection site swelling	0	0	1	1.2
Hematemesis	0	0	1	1.2

h. Conclusion: Maropitant administered at a dose of 1 mg/kg subcutaneously is effective for the prevention and treatment of cisplatin induced acute vomiting in dogs.

4. Clinical field study safety and effectiveness study to evaluate the effectiveness of maropitant at a dose of 1 mg/kg subcutaneously for the prevention and treatment of acute vomiting.

a. Study Title and Number: Field safety and effectiveness of subcutaneous and oral CJ-11,972 administered for emesis in dogs presented as veterinary patients. Study #1467C-60-01-597.

b. Type of Study: Field safety and effectiveness study.

c. Study Dates: August 18, 2003 – June 17, 2004.

d. Location(s) and Investigator(s):

Luis Alvarez, DVM
Miami, FL

Gary Brotze, DVM
New Braunfels, TX

Lynn Buzhardt, DVM
Zachary, LA

William Campaigne, DVM
Seguin, TX

William Craig, DVM
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Jeffrey Dizik, DVM
Lincoln Park, MI

N. Wayne Fry, DVM

Samuel Geller, VMD

Independence, MO

Quakertown, PA

Thomas Greene, DVM
Livonia, LA

David Hancock, DVM
Victor, NY

Larry Hendricks, DVM
Germantown, TN

Gayland Jones, DVM
Terre Haute, IN

Robert Kritsberg, DVM
Glendale, AZ

Andrea Komkov, DVM
Richardson, TX

Sharon Lachette, VMD
White Haven, PA

Stephen Ladd, DVM
Nashville, TN

David Lukof, VMD
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John McCormick, DVM
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Kathleen Neuhoff, DVM
Mishawaka, IN

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Springfield, MO

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Michael Shelton, DVM
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Herbert Utgard, DVM
Miami, FL

Philip VanVranken, DVM
Battle Creek, MI

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Baton Rouge, LA

e. General Design:

1) Purpose of Study: To characterize the field safety and effectiveness of maropitant administered by subcutaneous injection at a dosage of 1 mg/kg or orally at a minimum dosage of 2 mg/kg once daily, as needed, for up to 5 days for emesis in client-owned dogs 8 weeks of age or older at enrollment. The age of enrollment was later amended to 16 weeks of age or older at enrollment.[1]

[1] The minimum age of enrollment was changed from 8 to 16 weeks of age. See Safety Section for details.

2) Description of Test Animals: 275 dogs (144 females and 131 males) were enrolled in the study (206 administered maropitant and 69 administered placebo); 89 were mixed-breed dogs and 186 were pure-breed dogs. Dogs ranged from 7 weeks to 17 years of age at enrollment. Dogs weighed between 1.0 kg to 56.7 kg. All dogs were non-breeding and not pregnant. Overrepresented breeds included Labrador Retrievers (19), Dachshunds (15), Pit Bulls (14), Yorkshire Terriers (11), and Schnauzers (10). The dogs presented for acute vomiting for various reasons including parvovirus, gastroenteritis, pancreatitis, renal disease and other conditions. One hundred and ninety-nine dogs (111 females and 88 males) were included in the effectiveness analysis (145 treated with maropitant and 54 treated with placebo).

3) Control and Treatment Group(s):

Table 4.1: Control and Treatment Groups

Treatment Group	Dosage Form	Dose	Regimen	Route	# Dogs
T01 Placebo	Saline	0.1 mL/kg	Once on Day 0 and once daily as needed days 1 through 2-4	SC	69 dogs (36F, 33M)
	Placebo tablets	Equivalent to 2 mg/kg	Once daily as needed on Days 1 through 2-4	PO	
T02 Maropitant	Maropitant injectable	1.0 mg/kg	Once on Day 0 and once daily as needed days 1 through 2-4	SC	206 dogs (108F, 98M)
	Maropitant tablets	2 mg/kg	Once daily as needed on Days 1 through 2-4	PO	

4) Randomization: Dogs selected for the study were randomly allocated to treatment. Within each clinic, the study used a generalized, randomized block design with a one-way treatment structure. Block was based on sequence of animal presentation. Block size was 4 and within each block, the animals were enrolled in a 1 (placebo) to 3 (maropitant) ratio.

5) Masking: All study participants, with the exception of the Dispenser, were unaware of a dog's treatment allocation.

6) Inclusion Criteria: Patients were selected for the study from client-owned dogs presented to the veterinary practice. Patients enrolled in the study satisfied the following inclusion criteria:

- Presented to the veterinary hospital with a history of recent emesis for which use of an antiemetic was warranted.
- 16 weeks of age or older.[1]

- Owner provided consent to hospitalize his/her dog for the entire study period.

7) Exclusion Criteria: Patients were excluded from study enrollment if:

   - Any drug with antiemetic properties (metoclopramide, prochlorperazine, chlorpromazine, acepromazine, aminopentamide hydrogen sulfate, butorphanol, $5HT_3$ antagonists, and antihistamine H1 antagonists) had been administered within 24 hours of study enrollment or would need to be used concurrently during the study. Patients on long-term therapy with excluded drugs (i.e., antihistamines) were enrolled in the study if the excluded drug had not been administered within 24 hours of Study Day 0 and were not used concurrently during the study period.
   - A high degree of suspicion of gastrointestinal obstruction existed.
   - A high degree of suspicion of toxin ingestion existed.
   - The patient was severely compromised and not expected to survive the study period.

8) Drug Administration:

   a) Dosage amount, frequency, and duration: All treatments on Day 0 were administered subcutaneously. Subsequent treatments on Days 1, 2, 3, or 4 were administered orally or subcutaneously on an as needed basis as determined by the Examining Veterinarian. Administration of maropitant or placebo was limited to a single dose within each 24-hour period. Treatment doses were calculated according to the recorded Day 0 body weight. Subcutaneous maropitant treatments were administered at a dose of 1 mg/kg (0.1 mL/kg) body weight and oral doses were administered at a minimum of 2 mg/kg body weight (see Table 4.2). Equivalent volumes of saline and similar numbers and same sized placebo tablets were administered to dogs allocated to placebo treatment.

Table 4.2: Oral Dosing Table, Minimum of 2 mg/kg

Pounds (lb)	Kilogram (kg)	Tablet Size (mg)	Number of Tablets	Dosage Range (mg/kg)
2.2 – 8.8	1 – 4	16	0.5	2 – 8
>8.8 – 17.6	>4 - 8	16	1	2 – 4
>17.6 – 26.5	>8 – 12	24	1	2 – 3
>26.5 – 52.9	>12 – 24	24	2	2 – 4
>52.9 – 66.1	>24 – 30	60	1	2 – 2.5
>66.1 – 132.3	>30 – 60	60	2	2 – 4

Table 4.3 shows the sequence of formulation administered (tablet or injectable) for each day for the placebo and maropitant group. The most common administration sequence for both groups is a subcutaneous injection on Day 0 followed by an oral tablet on Day 1 with no further drug administration.

Table 4.3: Treatment administration sequence by study day.

Group	**Route of administration by study day**							
T01 Placebo	**Day0**	**Day1**	**Day2**	**Day3**	**Day4**	**Day5**	**# dogs**	**% dogs**
	SC						9	16.7%
	SC	PO					18	33.3%
	SC	PO	PO				2	3.7%
	SC	PO	PO	PO			1	1.8%
	SC	PO	PO	PO	PO		1	1.8%
	SC	SC					11	20.4%
	SC	SC	PO				3	5.6%
	SC	SC	SC				5	9.3%
	SC	SC	SC	SC			3	5.6%
	SC	SC	SC	SC	SC		1	1.8%
Total							**54**	**100%**
T02 Maropitant	SC						35	24.1%
	SC		PO				1	0.7%
	SC		SC				1	0.7%
	SC	PO					50	34.5%
	SC	PO	PO				8	5.5%
	SC	PO	PO	PO			6	4.1%
	SC	PO	PO	PO	PO		3	2.1%
	SC	SC					20	13.8%
	SC	SC		SC			2	1.4%
	SC	SC		SC	SC		1	0.7%
	SC	SC	PO				2	1.4%
	SC	SC	PO	PO			3	2.1%
	SC	SC	PO	PO	PO		1	0.7%

	SC	SC	SC				7	4.8%
	SC	SC	SC	PO	PO		1	0.7%
	SC	SC	SC	SC			2	1.4%
	SC	SC	SC	SC		SC	1	0.7%
	SC	SC	SC	SC	SC		1	0.7%
Total							**145**	**100%**

b) Route of administration: Oral and injectable.

c) Relationship to feeding: Not stated.

9) Variables Measured: Clinical pathology, evidence of vomiting, injection site evaluation and abnormal health were evaluated.

a) Clinical Pathology: Clinical pathology samples were collected prior to administration of maropitant or placebo on Day 0, prior to dosing, and repeated at study completion.

b) Evidence of Vomiting: Evidence of vomiting was recorded once or twice on Study Day 0 and twice daily thereafter. Evidence of vomiting was defined as vomitus observed in the cage or direct observation of a dog vomiting.

c) Injection Site Evaluation: For all subcutaneous injections, the injection site was observed once between 6 and 24 hours following the injection. Abnormal injection sites were observed weekly and observations were recorded until reasonable resolution or for up to 14 days post-treatment.

d) Abnormal Health: If any sign of abnormal health (other than vomiting or nausea) was observed at any time during the study the sign was recorded. Any sign of abnormal health was observed until resolution or up to 14 days post-treatment.

f. Results:

1. Evidence of Vomiting: Of the 199 dogs included in the statistical summary of effectiveness, 27 of 54 dogs (50%) in the placebo group displayed vomiting at some time during the study and 31 of 145 dogs (21.4%) in the maropitant-treated group displayed vomiting during the study period. Table 4.4 below shows the percent vomiting for each study day based upon the formulation administered (tablet or injectable).

Table 4.4: Percent Of Vomiting For Each Study Day, Based Upon Treatment and Route Of Administration.

Days	Treatment	Route	# Dogs	# Vomited	% Vomited
Day 0	Placebo (54)	SC	54	15	28%
	Maropitant(145)	SC	145 (143*)	14	10%
Day 1	Placebo (45)	PO	22	3	14%
		SC	23	16	70%
	Maropitant (108)	PO	67	2	3%
		SC	41	16	39%
Day 2	Placebo (16)	PO	7	2	29%
		SC	9	6	67%
	Maropitant (37)	PO	24	0	0%
		SC	13	8	62%
Day 3	Placebo (6)	PO	2	0	0%
		SC	4	1	25%
	Maropitant (21)	PO	14	0	0%
		SC	7	5	71%
Day 4	Placebo (2)	PO	1	0	0%
		SC	1	1	100%
	Maropitant (7)	PO	5	0	0%
		SC	2	1	50%
Day 5	Maropitant (1)	SC	1	0	0%

*2 dogs administered maropitant were not observed on day 0. Their vomiting status was unknown. 143 was used in the denominator for % vomited.

2. Injection Site Evaluations: Two hundred sixty-six injection sites were observed on 206 dogs treated with maropitant. No reactions were observed. One hundred four injection sites were observed on 69 dogs treated with placebo. Two were abnormal (1.9%).

3. Clinical Pathology: Summary statistics were calculated for 5 subgroups [parvoviral enteritis (26% of dogs enrolled), gastrointestinal disease (43%), acute pancreatitis (10%), renal disease (2%), and hepatic disease (2%)].

   a. Hematology: There were no treatment related effects seen.

   b. Serum Chemistry: There were no treatment related effects seen.

4. Study Completion: Eleven of 69 dogs (15.9%) administered placebo did not complete the study; 6 dogs due to lack of effectiveness, 2 dogs due to death and 3 dogs due to various reasons. Nineteen of 206 dogs (9.2%) administered maropitant did not complete the study: 5 due to lack of effectiveness, 11 due to death and 3 due to other reasons.

5. Concomitant Medications: Many medications were used concomitantly during the study. Many dogs received multiple medications. The most common concomitant medication was metronidazole. Other commonly used concomitant medications include: dextrose/Ringers solution IV, sodium chloride IV, amoxicillin, ampicillin, cefazolin, cephalexin, enrofloxacin, sulfamethoxazole/trimethoprim, famotidine, sucralfate, cimetidine, dexamethasone, ivermectin, ivermectin/pyrantel, pyrantel, lufenuron/milbemycin, milbemycin, moxidectin, vitamin B, and vaccines.

g. Adverse Reactions: All abnormal health observations seen during the study were recorded as adverse reactions (i.e. possibly related to treatment) if the clinical sign was observed after drug treatment and if the clinical sign was not present at the time the dog was originally presented and enrolled in the study.

Table 4.5: Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n=69)		Maropitant (n=206)	
	# dogs	% occur.	# dogs	% occur.
Death during study	4	5.8	10	4.9
Euthanized during study	0	0	2	1.0
Diarrhea	6	8.7	8	3.9
Hematochezia/bloody stool	5	7.2	4	1.9
Anorexia	2	2.9	3	1.5
Otitis/Otorrhea	0	0	3	1.5
Endotoxic Shock	1	1.4	2	1.0
Hematuria	0	0	2	1.0
Excoriation	0	0	2	1.0
Injection site reaction	2	2.9	0	0
Abdominal pain	0	0	1	0.5
Bradycardia	0	0	1	0.5
Conjunctival swelling/erythema	0	0	1	0.5
Depression	1	1.4	1	0.5
Dermatitis	1	1.4	1	0.5
Edema	0	0	1	0.5
Hemorrhage (abdominal)	0	0	1	0.5
Infection (unspecified)	0	0	1	0.5
Lethargy	1	1.4	1	0.5
Nasal discharge	1	1.4	1	0.5
Pain (localized)	0	0	1	0.5
Panting	1	1.4	1	0.5
Perineal pruritus	0	0	1	0.5
Polyuria/Polydipsia	0	0	1	0.5
Regurgitation	0	0	1	0.5
Rhinitis	0	0	1	0.5
Cardiovascular Shock	0	0	1	0.5
Ventral Erythema	0	0	1	0.5
Weakness	1	1.4	0	0.0
Weight loss	0	0	1	0.5
Total	26	37.6	55	18.5

h. Conclusion: Maropitant administered at a dose of 1 mg/kg subcutaneously once daily for up to 5 days is safe and effective for the prevention and treatment of acute vomiting in dogs.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study

1. Target Animal Safety Study in 16 week old dogs

a. Study Title and Number: Safety of CJ-11,972 administered to dogs once daily subcutaneously for 15 days. Study #5460N-36-04-290.

b. Type of Study: GLP Laboratory safety study

c. Study Dates: June 16 to July 27, 2004

d. Investigator and Location:

Dr. J. McKenna
Charles River Laboratories Biolabs Europe (CRLBLE).
Glenamoy, Ballina, Co. Mayo, Ireland

e. General Design:

1. Purpose of the Study: To evaluate the safety of maropitant when administered to dogs subcutaneously once daily for 15 days at 0, 1, 3, and 5 mg/kg.

2. Description of Test Animals: Twenty-eight male and 28 female Beagle dogs were used in this study (a minimum of 16 weeks of age on Day 0).

3. Control and Treatment Groups:

Table 1.1: Treatment and Control Groups Description

Treatment	Dosage (mg/kg)	Number and Sex of Animals	Clinical Observation Days
T01 (0.9% saline)	0	8 (4M, 4F)	0-14
T02 Maropitant	1	8 (4M, 4F)	0-14
T03 Maropitant	3	8 (4M, 4F)	0-14
T04 Maropitant	5	8 (4M, 4F)	0-14
T05 (0.9% saline)	0	8 (4M, 4F)	0-15, 22, 29, 36
T06 Maropitant	3	8 (4M, 4F)	0-15, 22, 29, 36
T07 Maropitant	5	8 (4M, 4F)	0-15, 22, 29, 36

4. Inclusion Criteria/Exclusion Criteria: Satisfactory physical examination, clinical pathology value, and general health observation.

5. Dose Administration: The dogs were dosed by subcutaneous injection once daily for 14 days at approximately the same time each day. The first daily dose was administered on Study Day 0 and the final dose was administered on Study Day 14.

6. Variables Measured: Health status was evaluated using data collected in physical examinations, health status observations (including injection site), and general observations as well as food consumption and weight gain over time. Additionally, samples were collected to assess laboratory values (serum chemistry panel, hematology, coagulation values, and urinalysis). Necropsy, histopathology, and bone marrow evaluation were carried out and tissue samples collected and analyzed.

7. Statistical Analyses Methodology: In all analyses, the experimental unit was the individual animal. Parameters measured once (organ weights) were analyzed for treatment effects by using a mixed linear model. For parameters 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. 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: any term involving sex was evaluated at $\alpha=0.05$ and any term involving treatment, but not sex, was evaluated at $\alpha=0.1$. When there was a significant treatment effect, follow-up pairwise comparisons were made between the vehicle control group and each treatment group by using linear contrasts with a significance level of 0.1.

f. Results: Maropitant injectable solution was well tolerated in all dogs. All dogs gained weight during the study without respect to treatment. Treatment-related findings consisted primarily of injection site lesions, detected by clinical, necropsy, and histopathology evaluations.

Clinical evaluation of the initial injection sites revealed mild pain on palpation in 2 dogs only, on the 10^{th} day after treatment. The other daily injection sites were found to be slightly thickened on 1 or more occasions in 6 dogs at 3 mg/kg (3X) and 5 dogs at 5 mg/kg (5X).

Injection site lesions were identified at necropsy in one dog at 1 mg/kg (1X), 4 dogs at 3 mg/kg (3X), and 6 dogs at 5 mg/kg (5X).

Histopathology examination identified lesions including minimal to mild granulomatous fibrinous inflammation, subcutaneous hemorrhage, and superficial eschar (1X and 3X lesions were not evaluated histologically). One female also had mild focal fibrinous necrosis and moderate subcutaneous edema.

The activated partial thromboplastin time (APTT) was prolonged (67.5 seconds, reference range 9-15 seconds) in one male dog in the 1 mg/kg group on Study Day 15. Relationship of the prolonged APTT to drug administration could not be determined.

g. Conclusion: Maropitant injectable solution (10 mg/mL) was well tolerated when administered subcutaneously to healthy 16-week-old dogs for 15 days at up to 5 mg/kg.

2. Target Animal Safety Study in 8 week old dogs

An additional study, "Safety of CJ-11,972 administered to dogs once daily subcutaneously for 15 days, Study" #1460N-60-01-585, with a design similar to Study #5460N-36-04-290 (described above) was conducted by Dr. Michael C. Savides at Ricerca Biosciences, LLC, in Concord, OH. The major differences in study design are that the subjects were 8 weeks rather than 16 weeks old on Study Day 0; the test subjects were weaned early and acclimated to the test facility for less than 2 weeks; the study used only 4 dogs per sex per treatment group; and did not include a "recovery" group. As shown in Table 2.1, in this study with 8 week old puppies there was an increased frequency and greater severity of bone marrow hypoplasia reported for dogs treated with elevated doses of maropitant. Other than the bone marrow hypoplasia, the overall results of the two studies are generally comparable. However, interpretation of the study outcome is complicated because the dogs were weaned early, minimally acclimated to the test facility, and some of the dogs in all groups in the study tested positive for coccidia.

Table 2.1: Frequency and Severity of Bone Marrow Hypoplasia in 8 Week Old Beagle Puppies Treated Subcutaneously Once Daily With CERENIA for 15 Days

	0 mg/kg/day								1 mg/kg/day								3 mg/kg/day								5 mg/kg/day							
Individual dogs	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
Hypoplasia score	1	†							2								3								2	3	4					

1 = minimal; 2 = slight/mild; 3 = moderate; 4 = moderately severe; 5 = severe
† One placebo Dog died on day 14 of the study. Diagnosis of suppurative pancreatitis and esophagitis was made.

Conclusion: The results of this study do not support the safe use of CERENIA in puppies 8-11 weeks of age.

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.

This information was provided by Pfizer Animal Health and found to be acceptable.

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.

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 acute vomiting in dogs.

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:

U.S. Patent Number	Date of Expiration
6,222,038	April 21, 2015
6,255,320	May 8, 2020

VII. ATTACHMENTS:

Facsimile Labeling:
- Package Insert
- Vial
- Carton