Date of Approval: January 29, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-262

CERENIA

(maropitant citrate)
Tablets
Dogs

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

Sponsored by:

Pfizer Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-262
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name(s):	CERENIA Tablets
D. Established Name(s):	Maropitant citrate
E. Pharmacological Category:	Antiemetic
F. Dosage Form(s):	Tablets
G. Amount of Active Ingredient(s):	16, 24, 60, and 160 mg of maropitant as maropitant citrate per tablet.
H. How Supplied:	CERENIA peach-colored tablets are scored with a break line. Each tablet is marked with "MPT" and the tablet strength on one side and the Pfizer logo on the other. Each tablet size is packaged in blister packs containing 4 tablets per perforated sheet.
I. How Dispensed:	Rx
J. Dosage(s):	Prevention of acute vomiting: administer a minimum of 2.0 mg/kg body weight once daily for up to 5 consecutive days. Prevention of vomiting due to motion sickness: administer a minimum of 8.0 mg/kg body weight once daily for up to 2 consecutive days.
K. Route(s) of Administration:	Oral
L. Species/Class(es):	Dogs
M. Indication(s):	For the prevention of acute vomiting in dogs. For the prevention of vomiting due to motion sickness 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:

Oral Dose of 2 mg/kg for the prevention of acute vomiting:
An oral dosage of 0, 1, 2, or 3 mg/kg maropitant was administered to 40 Beagles with 10 dogs per group (5 males, 5 females) to select the dosage for the prevention of acute vomiting in dogs. Dogs were administered maropitant 19 hours before administration of 70 mg/m^2 cisplatin. The mean number of emetic events experienced by the placebo dogs was 20.3 compared to 2.7, 1.1 and 0.5 for maropitant dogs at 1, 2, and 3 mg/kg, respectively. Dogs administered 1 mg/kg of maropitant orally exhibited more emetic events than dogs receiving 2 and 3 mg/kg of maropitant. An oral dose of 2 mg/kg maropitant was selected for further evaluation.

Oral Dose of 8 mg/kg for the prevention of vomiting due to motion sickness:
A series of three studies were conducted to characterize the dose of maropitant citrate for the prevention of vomiting due to motion sickness in dogs.

1) A three-phase European study entitled, "Efficacy and safety of CJ-11,972 in the prevention of motion sickness in dogs presented as veterinary patients." Study #5960C-85-01-246 was conducted at 23 veterinary clinics in Italy, France, and the UK. In Phase 1, 71 dogs with a history of motion sickness randomly received treatment with either a placebo or maropitant at a minimum dose of 2 mg/kg. Approximately (but not less than) 1 hour post-treatment the dogs were taken on a car journey of at least 30 minutes duration, during which any occurrence of vomiting was recorded by the owner. A planned interim data assessment determined that only 9 of the 37 dogs enrolled to date (24%) had vomited during the journey; insufficient numbers of placebo-treated dogs were vomiting as a result of the challenge. This suggested that either the journey was of insufficient duration to reliably induce vomiting in dogs prone to motion sickness, or that the severity of the condition was insufficient in the enrolled animals. Only animals that had demonstrated vomiting during the car journey in Phase 1 were selected for inclusion in subsequent phases.

   In phase 2, nine dogs that had vomited during Phase 1 were treated with maropitant at a minimum dose of 2 mg/kg, then taken on a car journey of at least 60 minutes duration, commencing approximately (but not less than) 1 hour post-treatment. Six of the 9 dogs treated with maropitant vomited during the car journey, indicating a lack of effectiveness of maropitant at 2 mg/kg for dogs prone to motion sickness.

In Phase 3, due to the apparent low effectiveness of the 2 mg/kg dose, maropitant was administered at a minimum dose of 8 mg/kg to 14 dogs that had vomited during Phase 1 (including 8 dogs that had completed Phase 2). The dogs were then taken on a car journey of at least 60 minutes duration commencing 1 hour post-treatment. Two of the 14 dogs treated with maropitant at a minimum dose of 8 mg/kg vomited during the car journey. For both of the dogs which vomited, tablets were found mostly undissolved in the vomitus. The results of this study indicated that a minimum dose of 2 mg/kg was insufficient to adequately prevent vomiting due to motion sickness during automobile travel. A minimum dose of 8 mg/kg suggested a trend toward effectiveness in preventing vomiting due to motion sickness when dogs were fasted 3 hours prior to travel and the drug was administered 1 hour prior to travel.

Dogs treated with maropitant experienced the following adverse reactions: depression, vomiting, diarrhea, inappetence and muscle tremors.

2) A crossover study entitled, "Field effectiveness and safety of CJ-11,972-10 in the prevention of motion sickness in dogs presented as veterinary patients." Study #1963C-60-02-628 was conducted, wherein 9 male and 8 female dogs of various breeds and mixed breeds were administered maropitant at a minimum dose of 8 mg/kg approximately 1 hour prior to transportation. Ten dogs vomited following treatment with placebo, and 3 dogs vomited following treatment with maropitant. Seven dogs vomited when treated with placebo, but did not vomit when treated with maropitant. Seven dogs did not vomit when treated with either placebo or maropitant. The study showed that maropitant citrate administered at a minimum dose of 8 mg/kg approximately 1 hour prior to transportation appeared to be effective in reducing the incidence of motion sickness-induced vomiting in dogs following a 1 hour journey by 70% relative to dogs which vomited following a placebo treatment. However, the sample size was insufficient to detect a significant treatment effect.

   The most common adverse events that occurred in dogs treated with maropitant were hypersalivation and retching (9 dogs). One dog each experienced flatulence, retching, and sedation/depression. Six placebo-treated dogs hypersalivated. One dog each experienced muscle tremors, retching and sedation/depression.

3) A pharmacokinetic study entitled, "Pharmacokinetics (PK) of CJ-11,972 following oral doses of 6 or 8 mg/kg to Beagle dogs." Study #1566E-60-02-642 was conducted to assist in the selection of an effective dose for the prevention of vomiting due to motion sickness in dogs. The two-period, two-sequence crossover study included the administration of non-final tablet sizes of maropitant citrate to fasted dogs (8 dogs per sequence). Plasma PK results indicated that peak plasma concentration (C_{max}), area under concentration curve

from 0-30 hrs (AUC_{0-30}), and elimination half-life ($T_{1/2}$) at 8 mg/kg were significantly larger than those at 6 mg/kg ($P < 0.05$). Dose-normalized C_{max} and AUC_{0-30} demonstrated that increasing the administered dose from 6 to 8 mg/kg provided a greater-than-dose-proportional increase in systemic drug exposure. Therefore, the 8 mg/kg dose level may be expected to provide a greater likelihood for effectiveness.

At the 8 mg/kg dose level, 2 dogs had intermittent mild tremors, one of which had tremors during both periods, and the other with tremors only during period 2. Vomiting occurred in 3 dogs dosed at 6 mg/kg and in 2 dogs dosed at 8 mg/kg (8 dogs/dose level/period) 0.5-1.5 hrs post-dose.

B. Substantial Evidence:

Prevention of Acute Vomiting

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

1. Dose Confirmation Laboratory study at a minimum dose of 2 mg/kg orally

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-60-01-586.

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

c) Study Dates: October 15 - 17, 2003

d) Location and Investigator(s):

Michael C. Savides, PhD
Ricerca, Inc., Concord, OH

e) General Design

1) Purpose of Study: To confirm the antiemetic effectiveness of a single minimum dose of 2 mg/kg maropitant administered to dogs orally approximately one 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 7 months old, weighing between 5.4 – 8.3 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	Oral	12 (6M, 6F)
T02 maropitant	2	Oral	12 (6M, 6F)

Dose range for maropitant was from 2.1 – 2.8 mg/kg orally.

4) Randomization: Dogs were allocated at random within sex to one of three batches, each batch containing 8 dogs (4 males and 4 females). Within each batch, animals were randomly allocated to treatment group 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 a minimum of 2 mg/kg maropitant or placebo 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: Oral.

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. *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 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: Ten of the 12 (83.3%) placebo-treated dogs exhibited vomiting during the one hour observation period following syrup of ipecac administration, exhibiting 1 to 4 emetic events. Four of the 12 (33.3%) maropitant-treated dogs exhibited vomiting after receiving syrup of ipecac administration, with 1 to 4 emetic events.

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** Exhibiting Vomiting	%	Number of Animals Exhibiting Vomiting	%
T01 placebo	12	2	16.7	10	83.3
T02 maropitant	12	8	66.7	4	33.3

The mean number of emetic events observed in the maropitant-treated dogs was significantly less (P = 0.0129) than that observed in the placebo-treated dogs.

3) VAS Scores for Nausea: A sex difference was seen, therefore, comparisons were made within sex. Least-squares mean VAS scores by timepoint for nausea following syrup of ipecac administration ranged from 5.3 to 44.2 for the placebo-treated females compared to a range of 0.0 to 6.3 for the maropitant-treated females. Differences were not observed for all timepoints, except VAS scores were lower for maropitant-treated females than those of placebo-treated females at the 18 minute timepoint and all timepoints from 27 through 51 minutes after syrup of ipecac administration. Least-squares mean VAS scores for nausea following syrup of ipecac administration ranged from 0.0 to 32.4 for the placebo-treated males compared to a range of 0.0 to 21.7 for the maropitant-treated males. No significant differences were observed in any VAS scores for males at any timepoints.

g) Adverse Reactions: None reported.

h) Conclusion: Maropitant at a minimum oral dose of 2 mg/kg was effective in the prevention of vomiting induced by syrup of ipecac.

2. Dose Confirmation Laboratory study at a minimum dose of 2 mg/kg orally

a) Study Title and Number: Dose confirmation of the efficacy of CJ-11,972 for apomorphine-induced emesis in dogs. Study #1960C-60-03-672.

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

c) Study Dates: December 10 - 12, 2003

d) Location and Investigator:

Michael C. Savides, PhD
Ricerca, Inc., Concord, OH

e) General Design

1) Purpose of Study: To confirm the antiemetic effectiveness of a single minimum dose of 2 mg/kg maropitant administered to dogs orally 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 7 months old, weighing between 6.3 – 8.4 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	Oral	12 (6M, 6F)
T02 maropitant	2	Oral	12 (6M, 6F)

Dose range for maropitant was from 2.05 – 2.9 mg/kg orally.

4) Randomization: Dogs were allocated at random within sex to one of 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 a minimum of 2 mg/kg maropitant or placebo on Day 0 once, approximately 1 hour before apomorphine administration. Dogs were administered apomorphine intravenously at a dosage of 0.01 mg/kg.

   b. Route of administration: Oral.

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 -7 through -1 and once prior to treatment on Day 0. A physical examination, including rectal temperature, thoracic auscultation, skin and hair coat, and general condition were performed on each dog on Day-5.

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 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 12 placebo-treated dogs exhibited vomiting during the 30 minute observation period following apomorphine administration exhibiting 1 to 4 emetic events. Four of the 12 maropitant-treated dogs exhibited vomiting after receiving apomorphine.

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

Treatment	#	Number of Animals **Not** Exhibiting Vomiting	%	Number of Animals Exhibiting Vomiting	%
T01 placebo	12	0	0	12	100
T02 maropitant	12	8	66.7	4	33.3

The mean number of emetic events observed in the maropitant-treated dogs was significantly less ($P < 0.0001$) 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 0 to 84.1 for the placebo-treated dogs compared to a range of 0.1 to 45.9 for the maropitant-treated dogs. VAS scores for maropitant-treated dogs were significantly lower ($P \leq 0.0011$) than those of placebo-treated dogs at the 3 and 6 minute timepoints. No significant differences in VAS scores were found at any other timepoints.

g) Adverse Reactions: None reported.

h) Conclusions: Maropitant at a minimum oral dose of 2 mg/kg was effective in the prevention of vomiting induced by apomorphine.

3. Field safety and effectiveness study to evaluate the effectiveness of maropitant at a minimum dose of 2 mg/kg orally for the prevention 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 San Antonio, TX	Jeffrey Dizik, DVM Lincoln Park, MI
N. Wayne Fry, DVM Independence, MO	Samuel Geller, VMD 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
Harleysville, PA

John McCormick, DVM
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Kathleen Neuhoff, DVM
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Springfield, MO

Susan Sallee, DVM
Grayslake, IL

Michael Shelton, DVM
Plano, TX

Roger Sifferman, DVM
Springfield, MO

Torry Steffen, DVM
Fort Wayne, IN

Herbert Utgard, DVM
Miami, FL

Philip VanVranken, DVM
Battle Creek, MI

Philip Waguespack, DVM
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 vomiting, for up to 5 days 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.[1]

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. Actual age of dogs at enrollment ranged from 7 weeks to 17 years of age. Dogs

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

weighed between 1.0 kg to 56.7 kg. All dogs were non-breeding and not pregnant. Over represented 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 3.1: 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 vomiting 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 3.2). Equivalent volumes of saline and similar numbers and same sized placebo tablets were administered to dogs allocated to placebo treatment.

Table 3.2: 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 3.3 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 3.3: 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.

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 3.4 below shows the percent vomiting for each study day based upon the formulation administered (tablet or injectable).

Table 3.4: 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 of the clinical pathology data 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 3.5: 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 minimum oral dose of 2 mg/kg once daily for up to 5 days, is safe and effective for the prevention of acute vomiting in dogs.

Prevention of Vomiting Due to Motion Sickness

Two field studies were conducted to confirm the dose of maropitant citrate for the prevention of vomiting due to motion sickness in dogs.

4. Field study at a minimum dosage of 8 mg/kg given 2 hours prior to travel

a) Study Title and Number: Field effectiveness and safety of CJ-11,972 at 8 mg/kg in the prevention of motion sickness in dogs presented as veterinary patients. Study #1963C-60-03-655

b) Type of Study: Field Study, Crossover Design

c) Study Dates: November 6, 2003 – November 4, 2004

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

Steven Aubry, DVM Brighton, MI	Jane Brawley, DVM Kansas City, KS
Gary Brotze, DVM New Braunfels, TX	Scott Buzhardt, DVM Zachary, LA
Bill Campaigne, DVM Seguin, TX	Randall Carpenter, DVM Greenville, MI
Terry Clekis, DVM Bradenton, FL	Wayne Fry, DVM Independence, MO
Samuel Geller, VMD Quakertown, PA	Thomas Greene, DVM Livonia, LA
David Kahn, DVM Dallas, TX	Scott Krick, DVM Sinking Spring, PA
Stephen Ladd, DVM Nashville, TN	Marc Leven, DVM Wyoming, MI
Dan McIlhany, DVM San Antonio, TX	Kathleen Neuhoff, DVM Mishawaka, IN
Dean Rund, DVM Springfield, MO	Roger L. Sifferman, DVM Springfield, MO
Jason Steinle, DVM Grapevine, TX	Susan Thompson, DVM Mt. Pleasant, SC
Charles Toben, DVM Glendale, AZ	Karen Updike, DVM Portage, MI

Philip Waguespack, DVM
Baton Rouge, LA

e) General Design

1. Purpose of Study: To evaluate the effectiveness and safety of maropitant citrate at a minimum dose of 8 mg/kg body weight, administered orally once 2 hours before transportation, for the prevention of vomiting due to motion sickness in dogs.

2. Description of Test Animals: One hundred thirty-eight dogs (61 males and 77 females) of various breeds and mixed-breeds, ranging in age from 11 weeks to 13 years old, and ranging in weight from 4.4 to 113.3 lbs (2 to 51.5 kg) on day of enrollment were included in the study.

3. Control and Treatment Group(s): This was a crossover study, wherein each dog was assigned to receive either placebo (T01) or active drug (T02) in Period 1, and after a minimum washout period of 10 days, receive the alternate treatment in Period 2.

Table 4.1. Treatment Groups

Tx Group	Dose[1]	Number and Sex of Animals
T01 Placebo	0 mg/kg	138 (77 F, 61 M)
T02 Maropitant	8 mg/kg	138 (77 F, 61 M)

[1] Minimum dose based on number and strength of tablets administered.

4. Randomization: Within each clinic, a randomized crossover treatment structure was used. Each dog was assigned to receive either placebo (T01) or maropitant (T02) in Period 1, and the alternate treatment in Period 2. Dogs were blocked on order of enrollment in each clinic with a block size of two with each treatment sequence represented.

5. Masking: All study participants, with the exception of the Dispenser, were unaware of a dog's treatment allocation. Placebo tablets were matched with maropitant tablets in appearance and packaging to ensure masking.

6. Inclusion Criteria: Participating dogs had a recent history of motion sickness; were suitable for the study when examined physically; and were non-breeding males and non-breeding, non-lactating females.

Diagnosis of motion sickness was based upon owner/designee information given to the clinical investigator.

7. Exclusion Criteria: Dogs less than 16 weeks of age[2], dogs treated with anti-emetic products in the preceding 5 days, or treated with products with emetic properties in the preceding 48 hours.

8. Drug Administration:

   a. Dosage amount, frequency, and duration: A minimum of 8 mg/kg, administered once 2 hours prior to travel. Dogs were administered the appropriate dose with tablets of the same strength to the nearest ½ tablet; thus, actual doses ranged from 8-12 mg/kg of body weight.

   b. Route of administration: Oral

   c. Relationship to feeding: Dogs were not fed within 1 hour of treatment and within 3 hours of the journey. Animals were not redosed if they vomited.

9. Variables Measured: Vomiting during journey

10. Statistical analysis: The proportion of dogs that did not vomit was modeled using a generalized linear mixed model using a logit link and a binomial error distribution. The model included treatment, sequence, and period as fixed effects and clinics and treatment-by-clinic interactions as random effects.

11. Criteria for Success/Failure: Criterion for success was that the dog did not exhibit vomiting during journey when treated with active drug.

f) Results

1. Clinical Observations and Exams: Animals were given physical exams by the clinical investigator prior to treatment in each Period to ascertain eligibility of animal for the study. Animals were given a physical exam at the end of Period 2, after journey.

[2] Protocol amendment changed the minimum age of enrollment from 8 to 16 weeks of age (see Safety Section for details).

Nothing abnormal related to the test drug was noted on physical exam, other than those clinical signs described below under "Adverse Reactions."

2. Vomiting during Journey: The study was conducted on 138 dogs at 23 clinics; however, sites with fewer than 4 dogs were excluded from the data analysis for effectiveness. After the exclusion of these sites, the remaining 122 dogs from 15 clinics were included in the effectiveness evaluation.

   Combining the results over the two treatment periods, 67 dogs out of 122 (55%) exhibited vomiting during the journey after being treated with placebo (T01). Following treatment with maropitant, 8 dogs out of 122 (6.6%) exhibited vomiting during the journey. Significantly fewer dogs experienced vomiting during the journey following maropitant treatment than following placebo treatment ($P < 0.0001$).

   Based on the fitted model, the estimated probabilities of not vomiting following treatment with either placebo or maropitant are given below. The 90% confidence intervals are also included to show the variability of the estimates and to give upper and lower bounds on the estimated probabilities.

Table 4.2 Probability of not vomiting following treatment.

Treatment	Pr(not vomiting), (90% CI)
Placebo	0.45, (0.37, 0.53)
Maropitant	0.93, (0.88, 0.96)

g) Adverse Reactions: The following adverse reactions were noted when animals were treated with maropitant:

Vomiting not associated with motion sickness: Six animals vomited after receiving the active drug, but before the journey started.

Hypersalivation: Ten animals salivated either during the journey or after the journey ended.

Sedation: One animal was mildly sedated after the journey ended.

The following table shows the number of adverse reactions noted in dogs treated with maropitant and placebo.

Table 4.3 Adverse Reactions

Adverse Reaction[1]	Maropitant (n=148)		Placebo (n=150)	
	No.	%	No.	%
Vomiting[2]	6	4.1	0	0
Salivation	10	6.8	8	5.3
Lethargy/Sedation	1	0.7	2	1.3
Retching	0	0	1	0.7

[1] Animals may have experienced more than one adverse reaction
[2] Not associated with motion sickness

h) Conclusion: The data from this study demonstrate that maropitant at a minimum oral dosage of 8 mg/kg given two hours prior to transportation is effective for the prevention of vomiting due to motion sickness in dogs.

5. Field study at a minimum dosage of 8 mg/kg given 10 hours prior to travel

a) Study Title and Number: Field effectiveness and safety of orally administered CJ-11,972 at 8 mg/kg, 10 hours before the journey, in the prevention of motion sickness in dogs presented as veterinary patients.
Study # 1963C-60-04-689

b) Type of Study: Field Study Crossover Design

c) Study Dates: October 26, 2004 – January 5, 2005

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

Bill Campaigne, DVM Seguin, TX	Samuel Geller, VMD Quakertown, PA
Dean Rund, DVM Springfield, MO	Philip VanVranken, DVM Battle Creek, MI

e) General Design

1. Purpose of Study: To evaluate the effectiveness and safety of maropitant citrate at a minimum dose of 8 mg/kg body weight, administered orally once 10 hours before transportation, for the prevention of vomiting due to motion sickness in dogs.

2. Description of Test Animals: Twenty-five dogs (13 males and 12 females) of various breeds and mixed-breeds, ranging in age from 4 months to 12 years of

age, and ranging in weight from 3.3 to 62.9 lbs (1.5 to 28.6 kg) were enrolled in the study.

3. Control and Treatment Group(s): This was a crossover study, wherein each dog was assigned to receive either placebo (T01) or active drug (T02) in Period 1, and after a minimum washout period of 11 days, receive the alternate treatment in Period 2.

Table 5.1 Treatment Groups

Tx Group	Dose[1]	Number and Sex of Animals
T01 Placebo	0 mg/kg	25 (12 F, 13 M)
T02 Maropitant	8 mg/kg	25 (12 F, 13 M)

[1] Minimum dose based on number and strength of tablets administered.

4. Randomization: Within each clinic, a randomized crossover treatment structure was used. Each dog was assigned to receive either placebo (T01) or maropitant (T02) in Period 1, and the alternate treatment in Period 2. Dogs were blocked on order of enrollment in each clinic with a block size of two with each treatment sequence represented.

5. Masking: All study participants, with the exception of the Dispenser, were unaware of treatment sequence. Placebo tablets were matched with maropitant tablets in appearance and packaging to ensure masking.

6. Inclusion Criteria: Participating dogs had a recent history of motion sickness; animals were suitable for the study when examined physically; dogs were non-breeding males and non-breeding, non-lactating females; the owner or designee gave informed consent for participation; the patient returned to the veterinary clinic after completing each journey; and owner or designee were able to administer medication to the dog as dispensed.

   Diagnosis of motion sickness was based upon owner/designee information given to the clinical investigator by owner or designee.

7. Exclusion Criteria: Dogs less than 16 weeks of age, dogs treated with anti-emetic products in the preceding 5 days, and dogs treated with products with emetic properties in the preceding 48 hours.

8. Drug Administration:

   a. Dosage amount, frequency, and duration: A minimum of 8 mg/kg body weight, administered once 10 hours prior to travel. Dogs were administered the appropriate dose with tablets of the same strength to the nearest ½ tablet. Actual doses ranged from 8-12 mg/kg of body weight.

      Treatment dosages were determined according to body weight taken at time of pre-treatment physical examination for both Periods 1 and 2. Owner administered treatment a minimum of one hour after returning from clinic, and approximately 10 hours before start of car journey.

   b. Route of administration: Oral

   c. Relationship to feeding: Dogs were not fed within 1 hour of treatment and within 3 hours of the journey.

9. Variables Measured: Physical examination and vomiting during journey

10. Statistical analysis: The proportion of dogs that did not vomit was modeled using a generalized linear mixed model using a logit link and a binomial error distribution. The model included treatment, sequence, and period as fixed effects and clinics and treatment-by-clinics interactions as random effects.

11. Criteria for Success/Failure: Criterion for success was that the dog did not vomit during journey when treated with active drug.

f) Results

Vomiting during Journey: The study was conducted on 25 dogs at 4 clinics; however, sites with fewer than 4 dogs were excluded from the data analysis for effectiveness. After exclusion of these sites, 22 dogs from 3 clinics were included in the effectiveness evaluation.

Combining the results over the two treatment periods, 16 dogs out of 22 (72.7%) exhibited vomiting during the journey after being treated with placebo (T01). Following treatment with maropitant, 3 dogs out of 22 (13.6%) exhibited vomiting during the journey. Significantly fewer dogs experienced vomiting during the journey following maropitant treatment than following placebo treatment ($P = 0.03$).

Based on the fitted model, the estimated probabilities of not vomiting following treatment with either placebo or maropitant are given below. The 90% confidence intervals are also included to show the variability of the estimates and to give upper and lower bounds on the estimated probabilities. Note that the confidence intervals are relatively wide, due to the small number of animals (22 dogs) in the study.

Table 5.2 Probability of not vomiting following treatment.

Treatment	Pr(not vomiting), (90% CI)
Placebo	0.23, (0.03, 0.77)
Maropitant	0.89, (0.35, 0.99)

g) Adverse Reactions: The following adverse reactions were noted when animals were treated with maropitant and placebo:

Table 5.3 Adverse Reactions

Adverse Reaction[1]	Maropitant (n=27)		Placebo (n=28)	
	No.	%	No.	%
Hypersalivation	7	25.9	5	17.9
Retching	0	0	1	3.6
Agitation	0	0	1	3.6

[1] Animals may have experienced more than one adverse reaction

h) Conclusion(s): The results of this study support the conclusion that maropitant at a minimum dosage of 8 mg/kg is effective in preventing vomiting due to motion sickness in dogs.

III. TARGET ANIMAL SAFETY:

A. Tolerance Study

1. Oral safety study for 7 days in young dogs

a. Study Title and Number: Safety of maropitant (CJ-11,972) administered as oral tablets for seven days to young dogs at dosages of 20 mg/kg and above. Study #5462E-36-02-265.

b. Type of Study: Laboratory safety study.

c. Study Dates: October 16 – November 28, 2002

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

Biological Laboratories Europe Ltd.
Glenamoy, Ballina Co. Mayo, Ireland
Investigator: Dr. U. Casserly

e. General Design

1. Purpose of Study: To assess the safety of maropitant when administered orally to young dogs once daily at and above 20 mg/kg for seven days.

2. Description of Test Animals: 14 male and 10 female Beagles, 11 to 25 weeks of age on Day 0. Dogs weighed 1.8 to 8.5 kg on Day -2.

3. Control and Treatment Group(s):

Table 1.1: Treatment and Control Groups Description

Tx Group	Dose (mg/kg)	Number and Sex of Animals
First Treatment Phase (Days 0 – 6)		
T01	0	8 (2F, 6M)
T02	20	8 (5F, 3M)
T03	30	8 (3F, 5M)
12 or 13 day wash-out		
Second Treatment Phase (Days 19 – 25 or 20 – 26)		
T01	0	8 (2F, 6M)
T02	40	8 (5F, 3M)
T03	50	8 (3F, 5M)

4. Randomization: The study used a randomized complete block design with a one-way treatment structure and three treatments. Twenty-four dogs were blocked according to their body weight. They were allocated to pens and assigned to one of three treatments (T01, T02, or T03).

5. Masking: Only individuals responsible for preparing and administering treatments were aware of the treatment allocation of each dog. The veterinarians, veterinary cardiologist, and all personnel performing general health observations, physical examinations, clinical observations, EKG and

clinical pathology analyses remained unaware of the allocation of animals to treatments throughout the study.

6. Inclusion Criteria/Exclusion Criteria: Healthy dogs based upon physical examination, body weight, ECG, and clinical pathology results.

7. Drug Administration:

   i. Dosage amount, frequency, and duration: The study was conducted in 2 phases; a first treatment phase (7 days) followed by a wash-out period of 12 or 13 days duration and a second treatment phase (7 days).

      Tablets were administered orally once daily for 7 days. In the first treatment phase, dogs were administered with either 0, 20 or 30 mg/kg on Study Days 0 through 6. In the second treatment phase, dogs were administered with either 0, 40, or 50 mg/kg on Study Days 19 or 20 through 25 or 26.

   ii. Route of administration: Orally.

   iii. Relationship to feeding: Dogs were fed after the two hour post-treatment clinical observation had been performed.

8. Variables Measured: General health observations, clinical observations, body weight, clinical pathology, and electrocardiograms.

   General Health Observations: During both treatment phases, general health observations were performed daily and for four hours ($\pm$30 minutes) after treatment administration.

   Clinical observations: Clinical observations were performed on each dog by a veterinarian within one hour prior to treatment administration and at 30 minutes ($\pm$10 minutes), 2 hours ($\pm$30 minutes) and 6 hours ($\pm$30 minutes) after each treatment administration. Clinical observations were also performed 24 hours ($\pm$1 hour) after the 7th treatment in both the first and second treatment phases.

   Body Weight: Body weights were obtained on Study Days -2, 18 or 19, and 27 or 28.

   Clinical Pathology: Blood samples were collected on Days -13, 6, 13 and 25 or 26.

Electrocardiograms (ECGs): ECGs using lead II were recorded for each dog on Days -15, 6, 13, and 25 or 26.

f. Results

1. Clinical Observations and Clinical Observations: There were no mortalities and all animals successfully completed the study. No concurrent medications were administered during the study.

   On Day 26, 1 male dog administered 50 mg/kg maropitant orally was found to be dull and thin on clinical examination and was given a fur fabric bedding mat, an infra-red lamp, and nutritional supplementation with a milk substitute. This animal remained on supplementary feeding and remained weak until Day 28 (study completion) when it was reported to be alert and active.

   Vomiting: Vomiting shortly after treatment administration was reported for dogs in all treatments. Most vomiting was a single emetic event, on the 1st or 2nd day of treatment only.

   Salivation: Salivation on the lips or chin was reported post-treatment for 2 dogs administered 50 mg/kg.

   Diarrhea/Loose Stool: During the second treatment phase, episodes of abnormal feces (generally yellow or white in color and soft but formed in consistency) were reported for one dog administered 0 mg/kg, 2 dogs administered 40 mg/kg, and 4 dogs administered 50 mg/kg.

Table 1.2: Number of Dogs Exhibiting Abnormal Clinical Signs During The First and Second Treatment Phases (Day 0 to 26)

Dose (mg/kg)	Vomiting	Abnormal Feces	Salivation	Depression	Weight Loss
0	2	1			
20 mg/kg	1				
30 mg/kg	1				
40 mg/kg	3	2			
50 mg/kg	5	4	2	1	3

2. Body Weights: Between Day -2 and Days 18 or 19, which included the first treatment phase, all dogs gained weight. However, during the second treatment phase, 1 dog administered 40 mg/kg and 3 dogs administered 50 mg/kg lost weight (range 2-11% loss). One dog administered 40 mg/kg had static weight. All other dogs in the study gained weight. However dogs administered 40 and 50 mg/kg gained less weight than dogs administered 0 mg/kg in the second treatment phase. One dog administered 50 mg/kg lost 20% of its Day 19 body weight.

3. Clinical Pathology

   i. Hematology: There was a trend toward increasing RBC, hematocrit, and hemoglobin values in dogs administered 50 mg/kg. There was 1 dog administered 40 mg/kg and 2 dogs administered 50 mg/kg with leukopenia characterized as a neutropenia.

   ii. Serum Chemistry: There was a trend toward decreasing phosphorous values in dogs administered 50 mg/kg. On Day 25/26, hypokalemia was seen in 1 dog administered 40 mg/kg and 3 dogs administered 50 mg/kg. One of the dogs administered 50 mg/kg also had decreased phosphorus, hypernatremia, weight loss and vomited on day 20. Another dog administered 50 mg/kg had hypernatremia on Day 25/26 and weight loss. On Day 25/26 there was one dog administered 40 mg/kg with hyperkalemia and hypocalcemia. On Day 26 one dog administered 50 mg/kg, had a slightly elevated ALP, decreased chloride, decreased creatinine, decreased phosphorus, hypokalemia and hyperproteinemia and weight loss. This is the same dog found dull and thin.

4. Electrocardiograms: No cardiac abnormalities of clinical importance were identified on examination of the ECG traces by the certified veterinary cardiologist. All dogs exhibited a sinus rhythm and no pathological dysrhythmias at all recordings throughout the study.

   Heart rate: The mean heart rate for all dogs was lower at the end of the first treatment phase on Day 6 than that recorded at the start of the acclimation period on Days -15 or -14. Similarly, mean heart rate at the end of the second treatment phase on Day 25 or 26 was lower than that observed during the wash-out period on Day 13; however the differences observed were more marked for both T02 and T03 than for dogs treated with placebo.

   QT interval: For all treatment groups (including placebo), mean QT interval corrected for heart rate changes was slightly longer at the end of the first and second treatment phases in a dose dependent manner. However, all values were within the normal ranges.

g. Conclusion: Maropitant tablets, administered at 20 and 30 mg/kg orally once a day for 7 days caused occasional vomiting in Beagle dogs. Maropitant tablets, administered at 40 and 50 mg/kg orally once a day for 7 days caused clinically relevant signs of weight loss, vomiting, soft stools, weakness, lethargy, salivation, and hypokalemia. Additionally, leukopenia characterized as a neutropenia, and a trend toward decreasing plasma phosphorus values were seen. Decreased heart

rate and prolonged corrected QT intervals were seen in all treatment groups in a dose dependent manner.

B. Margin of Safety:

1. Target Animal Safety Study for 2 mg/kg

a. Study Title and Number: Safety of CJ-11,972 Administered Orally to Dogs Once Daily for 15 Days. Study #1460N-60-04-679.

b. Type of Study: GLP Laboratory safety study

c. Study Dates: 14 June 2004 – 23 July 2004

d. Investigator and Location:

Ricerca Biosciences LLC., Concord, OH
Investigator: Michael C. Savides, PhD

e. General Design:

1. Purpose of the Study: To evaluate the safety of CJ-11,972 administered to dogs orally once daily for 15 days at 0, 2, 6, and 10 mg/kg.

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

3. Control and Treatment Groups:

Table 1.1: Treatment and Control Groups Description

Treatment	Dosage (mg/kg/day)	Number and Sex of Animals
T01	0	16 (8M, 8F)*
T02	2	8 (4M, 4F)
T03	6	16 (8M, 8F)*
T04	10	16 (8M, 8F)*

* Four dogs per sex were maintained after discontinuation of treatments on Day 15 ("recovery group"), and were to be necropsied on Day 43 if treatment-related bone marrow lesions were identified in dogs necropsied on Day 15.

4. Inclusion Criteria/Exclusion Criteria: Satisfactory clinical pathology value, satisfactory size, body weight, physical examination, or health observation.

5. Dose Administration: The animals were dosed orally once daily approximately 1 hour after feeding. A small volume of water was introduced into the mouth of the animal to aid in swallowing the tablet(s).

6. Variables Measured: Health status was evaluated using data collected in physical examinations, health status observations, and general observations as well as food consumption, and weight gain over time. Additionally, lab values (serum chemistry panel, hematology, coagulation values, and urinalysis) and necropsy with histopathology and bone marrow evaluation were performed and the results 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: Food consumption in dogs receiving maropitant at 2 mg/kg/day and 10 mg/kg/day was lower (approximately 13% and 11%, respectively) than placebo. Body weights in dogs treated with maropitant at 2, 6 and 10 mg/kg/day were slightly lower (approximately 2%) than placebo. Neither effect on feed consumption or body weight continued after the end of dosing in surviving dogs for the 6 and 10 mg/kg/day groups. All other findings in clinical pathology and histopathology were considered incidental and unrelated to treatment.

g. Conclusions: Maropitant caused decreases in food consumption and body weight that were not dose-dependent and did not persist after cessation of treatment. This study supports the safe use of maropitant citrate at 2 mg/kg/day for 5 days in 16 week old dogs.

2. Target Animal Safety Study for 2 mg/kg in 8 week old Beagles

An additional study, "Safety of CJ-11,972 administered orally to dogs once daily for 15 days", Study #1460N-60-03-663, with a design similar to Study #1460N-60-04-679 (described above) was conducted at the same facility by the same investigator. The major differences in study design were 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; this study used only

4 dogs per sex per treatment group; and it did not include a "recovery" group. In this study with 8 week old puppies, there was a greater severity of bone marrow hypoplasia reported for dogs treated with elevated doses of maropitant than control dogs (Table 2.1). 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, some of the dogs in all groups in the study tested positive for coccidia, and some of the dogs in the study tested positive for canine parvovirus.

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

	0 mg/kg/day								2 mg/kg/day								6 mg/kg/day								10 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	1	2						1	1	2	2					1	3							4	4	4					

1 = minimal; 2 = slight/mild; 3 = moderate; 4 = moderately severe; 5 = severe

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

3. Target Animal Safety Study for 8 mg/kg

a. Study Title and Number: Safety of CJ-11,972 Administered Orally to Dogs Once Daily for 6 Consecutive Days at 0, 1X, and 3X the Motion Sickness Dose of 8 mg/kg. Study #1460N-60-04-680.

b. Type of Study: GLP laboratory study.

c. Study Dates: April 2, 2004 to March 21, 2005.

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

Ricerca Biosciences, LLC, Concord, Ohio
Investigator: Michael C. Savides, PhD

e. General Design

1. Purpose of Study: To evaluate the safety of maropitant tablets when administered orally to young Beagle dogs once daily for 6 consecutive days at 0, 8, and 24 mg/kg.

2. Description of Test Animals: Forty Beagle dogs (20 males and 20 females) were 16.7 – 18.0 weeks old and weighed between 3.8 and 6.35 kg on Day 0.

3. Control and Treatment Group(s):

Table 3.1: Treatment and Control Groups Description

Tx Group	Dose (mg/kg)	Number and Sex of Animals
T01	0 mg/kg	16 (8M, 8F)*
T02	8 mg/kg (8 – 8.78)	8 (4M, 4F)
T03	24 mg/kg (24 – 24.35)	16 (8M, 8F)*

*4 dogs per sex were maintained after discontinuation of experimental treatments on Day 6 (recovery group).

4. Randomization: The dogs were allocated randomly within block to treatment and necropsy order on Day -2. Blocking was based on sex, body weight and cage location.

5. Masking: The veterinarians conducting physical examinations and clinical observations and other personnel involved in dosing and making general health observations did not know the allocation of animals to treatment. The individuals involved in the necropsies, including the pathologist, also were masked to treatment. The pathologist reading the histology slides was masked to treatment until the slides from the control and high dose groups were read and the histopathological findings recorded.

6. Inclusion Criteria/Exclusion Criteria: Satisfactory, normal, healthy dogs selected based on age, physical findings (weight, body condition, health observations, physical examination), clinical pathology findings, behavior, and acclimatization.

7. Drug Administration:

   a. Dosage amount, frequency, and duration: Each dog was dosed once daily for 6 days (Days 0 through 5) with 0, 8 or 24 mg/kg maropitant.

   b. Route of administration: Orally.

   c. Relationship to feeding: Fed state. All dogs were administered the dose approximately 1 hour after feeding.

8. Variables Measured: General health observations, clinical examinations, feed consumption, body weight, clinical pathology and necropsy.

    a. General Health Observations and Clinical Examinations: General health observations of all dogs were observed at least twice daily from Day -26 until the end of the study. Clinical observations were made by a veterinarian once daily at a time distinct from the general health observations on Days -21, -14, -7, from Day -3 until Day 6, and on Days 13 and 20.

    b. Feed consumption: Feed consumption for all dogs was recorded at least twice daily. The dogs were offered fresh food at least daily. Feed consumption was also measured for the recovery groups from approximately Days 16 – 20.

    c. Body Weights: All dogs were weighed on Days -21, -14, -7, -3, 0 and Day 6. In addition, the recovery groups were weighed on Days 13 and 20.

    d. Clinical Pathology: Blood and urine was collected from each dog on Day -7 for baseline/evaluation tests, and on Day 6. Clinical pathology tests were conducted weekly on the recovery groups on Days 12, 19 and 26. Feces were collected on approximately Days -28, -8 and 5.

    e. Necropsy: All dogs (excluding the recovery groups) were humanely euthanized on Day 6, and a full necropsy was performed. Tissues from dogs in the placebo and 24 mg/kg groups plus bone marrow from the 8 mg/kg group were evaluation by a veterinary pathologist.

f. Results

1. General Health Observations and Clinical Examinations: Three dogs administered 24 mg/kg weighed less on Day 6 than on Day 0 but gained weight during the recovery phase. However, thin body mass was reported on Day 13 during the recovery phase for these dogs. One dog administered 24 mg/kg had no appetite on Days 3, 4, and 5 prior to dosing for that day. This same dog was lethargic on Days 4 and 5, had weight loss on Day 6 and a thin body mass on Day 13. One dog administered 24 mg/kg vomited one time on Day 0 prior to dosing. One dog administered 8 mg/kg vomited one time on Day 3 prior to dosing. Loose stools and diarrhea were observed in all treatment

groups. Dermatitis/alopecia and soft stools/diarrhea were observed both during the acclimation period and during the treatment phase.

2. Feed Consumption: There was a test-article related reduction in feed consumption. Feed consumption was similar between treatments prior to dosing. On Day 6, feed consumption was lower in the 24 mg/kg group compared to the placebo group. In the recovery group after Day 6, the dogs administered 24 mg/kg resumed eating about the same daily quantity as the placebo group.

3. Body Weights: There was a dose-related decrease in body weight. Mean body weights decreased in the 8 and 24 mg/kg groups and increased in the placebo group on Day 6 compared to Day 0.

Table 3.2: Average Weight Gain (kg) Per Treatment Group

Group	Day -21 to 0	Day 0 to 6	Day 6 to 20
T01	0.78	0.04	0.9
T02	0.65	-0.01	N/A
T03	0.65	-0.36	0.9

4. Clinical Pathology

   i. Hematology: Hemoconcentration of RBC's and HCT was seen in dogs treated with 24 mg/kg. The hematocrit on Day 6 was 9.5% higher than on Day -8. Neither the placebo group nor dogs administered 8 mg/kg experienced a change in hematocrit.

   ii. Serum Chemistry: On Day 6, decreased phosphorus was seen in 8 of 16 dogs administered 24 mg/kg. Other changes seen were not considered clinically relevant or treatment related.

   iii. Urinalysis: No treatment related findings were seen on the urinalysis.

5. Pathology

   i. Gross Post-Mortem exam: There were no treatment related findings upon gross necropsy. Testes weights were less in dogs administered 24 mg/kg compared to placebo dogs. Liver weight was decreased in dogs administered 8 and 24 mg/kg compared to placebo dogs.

   ii. Histopathology: No treatment related findings were seen on histopathology; therefore, tissues from dogs administered 8 mg/kg were not evaluated. Three dogs administered 24 mg/kg and 2 dogs

administered placebo had a decrease in the amount of hepatocellular glycogen compared to the amount noted in other dogs. In the endocrine tissues, cysts were noted in the pituitary of 3 dogs administered 24 mg/kg and 1 placebo dog.

Bone marrow was comparable in all groups and appeared to be normal. There was a decrease in the mean proportion of erythroid cells and an increase in the mean proportion of total granulocytic cells in dogs receiving 24 mg/kg compared to placebo dogs, resulting in higher mean Myeloid:Erythroid (ME) ratios. These differences were due to 3 dogs (2 males, 1 female) administered 24 mg/kg which had a lower proportion of total erythroid cells, with a resultant increase in the proportion of total granulocytic cells. For these animals, the reticulocyte counts in the peripheral blood were lower than the range of the control animals, indicating a lower production of erythroid cells at 24 mg/kg compared to controls.

g. Conclusion: This study supports the safe use of maropitant at 8 mg/kg orally for 2 days in 16 week old dogs. Maropitant administered at 8 mg/kg orally for 6 days to 16 week old Beagle dogs caused decreased body weight. Maropitant administered at 24 mg/kg orally for 6 days to 16 week old Beagle dogs (8 males and 8 females) caused decreased food consumption, body weight, liver and testis weight, lethargy, decreased phosphorus, and increased RBC count.

4. Target Animal Safety Study for 8 mg/kg in 8 week old Beagles

An additional study, "Safety of CJ-11,972 administered PO to dogs once daily for 6 consecutive days at 0, 1X, and 3X the motion sickness dose of 8 mg/kg", Study #1460N-60-03-656, with a design similar to Study #1460N-60-04-680 (described above) was conducted at the same facility by the same investigator. The major differences in study design were 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; this study used only 4 dogs per sex per treatment group; and this study did not include a "recovery" group. In this study with 8 week old puppies, one dog treated with 24 mg/kg/day of maropitant died suddenly on treatment day 2 and no definitive cause of death was determined. Additionally, increased frequency and severity of bone marrow hypoplasia and lymphoid depletion of spleen, thymus, and lymph nodes was reported for dogs treated with elevated doses of maropitant (Table 4.1). Other than the bone marrow hypoplasia and lymphoid depletion, the overall results of the two studies are generally comparable. However, interpretation of these study results is complicated by reports that the dogs used in the study were weaned early, minimally acclimated to the test facility, and many of the dogs in the study tested positive for coccidia. Additionally, some dogs in the study tested positive for

canine parvovirus, however, clinical parvoviral disease was not definitively diagnosed.

Table 4.1: Frequency and Severity of Bone Marrow Hypoplasia in 8 Week Old Beagle Puppies Treated Once Daily for 6 Days With CERENIA Oral Tablets

	0 mg/kg/day								8 mg/kg/day								24 mg/kg/day							
Individual dogs	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	†	5	6	7	8
Bone Marrow Hypoplasia					2				2	1					1		3	2	5		5	3		1
Lymphoid Depletion, Thymus	3			2	2			1				1	2	1			2	3	4	1	4	1	2	2
Lymphoid Depletion, Spleen																	3	2	2	4	3		2	
Lymphoid Depletion, Cervical Lymph Node																				4		2		3
Lymphoid Depletion, Mediastinal Lymph Node				2	2												2	3	4	2	2	3		2
Lymphoid Depletion, Mesenteric Lymph Node																	2		2	3	1			

1 = minimal; 2 = slight/mild; 3 = moderate; 4 = moderately severe; 5 = severe
† One puppy died on day 2 of the study. No cause of death was determined.

Conclusion: The results of this study do not support the safe use of CERENIA in puppies 8-10 weeks of age.

5. European Field Safety Study

Two hundred and thirteen dogs with a history of motion sickness were enrolled in a field study in Europe (133 dogs in France, 37 in Italy, and 43 in the UK) to evaluate maropitant tablets for the prevention of vomiting due to motion sickness. One hundred and six dogs were administered placebo and 107 dogs were administered 8 mg/kg maropitant tablets orally on Days 0 and 1. Dogs were fasted at least 3 hours prior to the start of the car trip and at least 2 hours prior to tablet administration. The owners transported their dog by car in a trip that lasted at least 60 minutes on Day 0 and at least 10 minutes on Day 1. The following adverse reactions, not considered related to motion sickness, were reported during the study.

Table 5.1 Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n = 106)		Maropitant (n=107)	
	# dogs	% occur	# dogs	% occur
Vomiting	4	4	10	9
Drowsiness/Lethargy/Apathy	1	1	8	8
Hypersalivation	2	2	5	5
Anxiety	0	0	2	2
Trembling/Tremors	0	0	2	2
Inappetence	0	0	2	2
Mucus in stool	0	0	1	1

Conclusions: This study supports the safe use of maropitant tablets when administered orally at 8 mg/kg once daily for 2 consecutive days under actual conditions of use for the prevention of vomiting due to motion sickness.

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 Tablets:

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

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 Tablets, when used according to the label, are safe and effective for the prevention of acute vomiting and the prevention of vomiting due to motion sickness.

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 and vomiting due to motion sickness in dogs.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

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
Blister Package (16 mg, 24 mg, 60 mg, 160 mg)
Carton (16 mg, 24 mg, 60 mg, 160 mg)
Display Carton (16 mg, 24 mg, 60 mg, 160 mg)