Cerenia® (maropitant citrate)

Tablets and Injectable Solution

Antiemetic

CERENIA Tablets

For oral use in dogs only

CERENIA Injectable

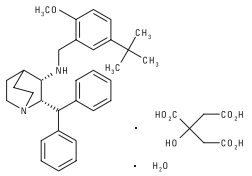
For subcutaneous injection in dogs and cats

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

Maropitant is a neurokinin (NK_1) receptor antagonist that blocks the pharmacological action of substance P in the central nervous system (CNS). Maropitant is the non-proprietary designation for a substituted quinuclidine. The empirical formula is $C_{32}H_{40}N_2O \cdot C_6H_8O_7 \cdot H_2O$ and the molecular weight 678.81. The chemical name is (2*S*,3*S*)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate. Each mL of CERENIA Injectable Solution contains 10 mg maropitant, 63 mg sulphobutylether-beta-cyclodextrin, 3.3 mg meta-cresol and water for injection.

The chemical structure of maropitant citrate is:



INDICATIONS:

CERENIA (maropitant citrate) Tablets are indicated for the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs. CERENIA (maropitant citrate) Injectable Solution is indicated for the prevention and treatment of acute vomiting in dogs and for the treatment of vomiting in cats.

DOSAGE AND ADMINISTRATION:

TABLETS (dogs only)

For Prevention of Acute Vomiting in dogs 8 weeks and older

Administer CERENIA Tablets orally at a minimum dose of 2 mg/kg (0.9 mg/lb) body weight once daily for up to 5 consecutive days.

Prevention of Acute Vomiting
Minimum of 2 mg/kg BW Dosing

Dog body weight		Number of Tablets		
Pounds	Kilograms	16 mg	24 mg	60 mg
2.2 – 8.8	1.0 – 4	½		
8.9 – 17.6	4.1 – 8	1		
17.7 – 26.4	8.1 – 12		1	
26.5 – 52.8	12.1 – 24		2	
52.9 – 66	24.1 – 30			1
66.1 – 132	30.1 – 60			2

CERENIA Tablets may be used interchangeably with CERENIA Injectable Solution for once daily dosing for the prevention of acute vomiting.

For Prevention of Vomiting Due to Motion Sickness in dogs 16 weeks and older

Administer CERENIA Tablets orally at a minimum dose of 8 mg/kg (3.6 mg/lb) body weight once daily for up to 2 consecutive days. Dogs should be fasted 1 hour prior to administration of CERENIA Tablets. Administer CERENIA Tablets 2 hours prior to travel.

Prevention of Vomiting Due to Motion Sickness
Minimum of 8 mg/kg BW Dosing

Dog body weight		Number of Tablets			
Pounds	Kilograms	16 mg	24 mg	60 mg	160 mg
2.2	1	½			
2.3 – 3.3	1.1 – 1.5		½		
3.4 – 4.4	1.6 – 2	1			
4.5 – 6.6	2.1 – 3		1		
6.7 – 8.8	3.1 – 4	2			
8.9 – 13.2	4.1 – 6		2		
13.3 – 16.5	6.1 – 7.5			1	
16.6 – 22	7.6 – 10				½
22.1 – 33	10.1 – 15			2	
33.1 – 44	15.1 – 20				1
44.1 – 66	20.1 – 30				1½
66.1 – 88	30.1 – 40				2
88.1 – 132	40.1 – 60				3

INJECTABLE (dogs and cats)

For Prevention of Acute Vomiting in dogs 8 weeks and older and for the Treatment of Vomiting in cats 16 weeks and older

Administer CERENIA Injectable Solution subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 1 mL/10kg (1 mL/22 lb) of body weight once daily for up to 5 consecutive days. Use of refrigerated product may reduce the pain response associated with the injection.

For dogs, CERENIA Injectable Solution may be used interchangeably with CERENIA Tablets for once daily dosing for the prevention of acute vomiting.

INFORMATION FOR USE:

CERENIA Tablets have been shown to be effective for the prevention of vomiting (see **EFFECTIVENESS**), however where the frequency of vomiting is high, orally administered CERENIA may not be absorbed before the next vomiting event occurs. Therefore, initiation of therapy with CERENIA Injectable Solution is recommended. If vomiting persists despite treatment, the case should be re-evaluated. CERENIA is most effective in preventing vomiting associated with chemotherapy if administered prior to the chemotherapeutic agent.

WARNINGS:

Not for use in humans. Keep out of reach of children. In case of accidental ingestion, 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.

In puppies younger than 11 weeks of age, histological evidence of bone marrow hypocellularity was observed at higher frequency and greater severity in puppies treated with CERENIA compared to control puppies. In puppies 16 weeks and older, bone marrow hypocellularity was not observed (see **Animal Safety**).

PRECAUTIONS:

The safe use of CERENIA has not been evaluated in dogs or cats used for breeding, or in pregnant or lactating bitches or queens. The safe use of CERENIA has not been evaluated in dogs or cats with gastrointestinal obstruction, or dogs or cats that have ingested toxins.

Use with caution in patients with hepatic dysfunction because CERENIA is metabolized by CYP3A enzymes (see **Pharmacokinetics**). Use with caution with other medications that are highly protein bound. The concomitant use of CERENIA with other protein bound drugs has not been studied in dogs or cats. Commonly used protein bound drugs include NSAIDs, cardiac, anticonvulsant, and behavioral medications. The influence of concomitant drugs that may inhibit the metabolism of CERENIA has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

CERENIA causes dose related decreases in appetite and body weight (see **ANIMAL SAFETY**). To maximize therapeutic potential of CERENIA, the underlying cause of vomiting should be identified and addressed in dogs receiving CERENIA.

ADVERSE REACTIONS:

DOGS:

In a US field study for the prevention and treatment of vomiting associated with administration of cisplatin for cancer chemotherapy, the following adverse reactions were reported in 77 dogs treated with CERENIA Injectable Solution at 1 mg/kg subcutaneously or 41 dogs treated with placebo:

Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n=41)		CERENIA (n=77)	
	# dogs	% occur	# dogs	% occur
Diarrhea	1	2.4	6	7.8
Anorexia	0	0	4	5.2
Injection site reaction (swelling, pain upon injection)	0	0	3	4
Lethargy	1	2.4	2	2.6

Adverse reactions seen in a European field study included ataxia, lethargy and injection site soreness in one dog treated with CERENIA Injectable Solution.

The following adverse reactions were reported during the course of a US field study for the prevention and treatment of acute vomiting in dogs treated with 1 mg/kg CERENIA Injectable Solution subcutaneously and/or CERENIA Tablets at a minimum of 2 mg/kg orally once daily for up to 5 consecutive days:

Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n=69)		CERENIA (n=206)	
	# dogs	% occur	# dogs	% occur
Death during study	4	5.8	10	4.9
Euthanized during study	0	0	2	1
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
Hematuria	0	0	2	1
Excoriation	0	0	2	1

Other clinical signs were reported but were <0.5% of dogs.

The following adverse reactions were reported during US studies for the prevention of vomiting due to motion sickness in dogs treated with CERENIA Tablets at a minimum of 8 mg/kg orally one time. Dogs may have experienced more than one of the observed adverse reactions.

Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n=195)		CERENIA (n=208)	
	# dogs	% occurrence	# dogs	% occurrence
Hypersalivation	19	9.7	26	12.5
Vomiting[1]	0	0	11	5.3
Muscle Tremors	1	0.5	2	1
Sedation/Depression	3	1.5	2	1
Retching	3	1.5	1	0.5
Flatulence	0	0	1	0.5

[1] Not associated with motion sickness

The following adverse reactions were reported during a European field study for the prevention of vomiting due to motion sickness in dogs treated with CERENIA Tablets at a minimum of 8 mg/kg orally once daily for 2 consecutive days. Dogs may have experienced more than one of the observed adverse reactions.

Frequency of Adverse Reactions by Treatment

Adverse Reaction	Placebo (n=106)		CERENIA (n=107)	
	# dogs	% occurrence	# dogs	% occurrence
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

CATS:

The following adverse reactions were reported during the course of a US field study for the treatment of vomiting in cats treated with 1 mg/kg CERENIA Injectable Solution subcutaneously once daily for up to five consecutive days:

Frequency of Adverse Reactions by Treatment

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

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

[2] Cat objected to the injection by retreating and vocalizing

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

Post-Approval Experience

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events for CERENIA Tablets are listed in decreasing order of reporting frequency in dogs: depression/lethargy, anorexia, hypersalivation, vomiting, diarrhea, ataxia, and trembling.

Cases of ineffectiveness have been reported

The following adverse events for CERENIA Injectable use in dogs are listed in decreasing order of reporting frequency in dogs: Pain/vocalization upon injection, depression/lethargy, anorexia, anaphylaxis/anaphylactoid reactions (including swelling of the head/face), ataxia, convulsions, and hypersalivation.

Cases of death (including euthanasia) have been reported.

The following adverse events for CERENIA Injectable use in cats, reported since 2007, are listed in decreasing order of reporting frequency in cats: depression/lethargy, anorexia, injection site pain, and hypersalivation.

For a complete listing of adverse reactions for CERENIA Tablets reported to CVM see:
http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055369.htm

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Pfizer Animal Health at 1-800-366-5288.

CLINICAL EXPERIENCE:

CERENIA Tablets

For motion sickness, prolonged fasting before administration should be avoided. Feeding dogs a small amount of food one hour prior to the administration of 8 mg/kg of CERENIA Tablets may mitigate vomiting that may occur within two hours post-dosing and prior to travel.

CERENIA Injectable Solution

The pain or vocalization upon injection resolves within minutes without treatment. Administration of CERENIA Injectable Solution at refrigerated temperature may mitigate this response (see **DOSAGE AND ADMINISTRATION**). Allergic reactions typically resolve with treatment within 48 hours after discontinuing CERENIA administration.

CLINICAL PHARMACOLOGY:

Pharmacodynamics:

Vomiting is a complex process coordinated centrally by the emetic center which consists of several brainstem nuclei (area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus) that receive and integrate sensory stimuli from central and peripheral sources and chemical stimuli from the circulation and the cerebrospinal fluid. Maropitant is a neurokinin 1 (NK1) receptor antagonist which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. Substance P is found in significant concentrations in the nuclei comprising the emetic center and is considered the key neurotransmitter involved in emesis.[1] By inhibiting the binding of substance P within the emetic center, maropitant provides broad-spectrum effectiveness against neural (central) and humoral (peripheral) causes of vomiting. *In vivo* model studies in dogs have shown that maropitant has antiemetic effectiveness against both central and peripheral emetogens including apomorphine, cisplatin, and syrup of ipecac.

[1]Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. [Review] [60 refs]. Drugs. 2000;60:533-46.

Pharmacokinetics

CERENIA is formulated using sulphobutylether-β-cyclodextrin (SBECD), which exhibits enhanced binding to maropitant at refrigerated temperatures. The enhanced binding affinity reverses rapidly upon warming.

DOGS:

The pharmacokinetic characterization associated with maropitant after oral (PO) or subcutaneous (SC) administration in adult Beagle dogs is provided in the table below.

Pharmacokinetic Parameters in Beagle Dogs (Mean±SD or range)			
	SC at 1 mg/kg (n=6)	PO at 2 mg/kg (n=8)	PO at 8 mg/kg (n=8)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	860±137	561±322	7840±5600
C_{max} (ng/mL)	92±34	81±32	776±604
$T_{1/2}$ (hr)	8.84 (6.07-17.7)	4.03 (2.48-7.09)	5.46 (3.39-7.65)
T_{max} (hr)	0.75±1.11	1.9±0.5	1.7±0.7

The absolute bioavailability of maropitant was much higher following SC injection (91% at 1 mg/kg) than after PO administration (24% at 2 mg/kg). Oral bioavailability may be underestimated due to the presence of nonlinear kinetics and the resulting longer T1/2 seen after intravenous (IV) administration. Although hepatic first-pass metabolism contributed to the relatively low bioavailability after an oral dose, prandial status does not significantly affect the extent of oral bioavailability. Greater than dose-proportional drug exposure can be expected with an increase in dose (1-16 mg/kg PO). Systemic clearance of maropitant following IV administration was 970, 995, and 533 mL/hr/kg at doses of 1, 2 and 8 mg/kg, respectively. An accumulation ratio of 1.5 was observed following once-daily use of maropitant for five consecutive days at 1 (SC) or 2 mg/kg (PO). Urinary recovery of maropitant and its major metabolite was minimal (<1% each). The hepatic metabolism of maropitant involves two cytochrome P-450 isoenzymes: CYP2D15 and CYP3A12. Based on in vitro enzyme kinetics data, it is believed that the non-linear kinetics may be partially associated with saturation of the low capacity enzyme (CYP2D15). However as doses increase (20-50 mg/kg PO), dose proportionality is re-established. Based upon *in vitro* enzyme kinetics, involvement of a high capacity enzyme (CYP3A12) may contribute to this return to dose linearity. Plasma protein binding of maropitant was high (99.5%).

Based on differences in plasma trough concentrations from a single study, the exposure of 10 week old puppies to maropitant may be lower than that observed in adult dogs, particularly after doses of 1 or 2 mg/kg.

CATS:

The pharmacokinetic profile of maropitant when administered as a single subcutaneous dose of 1 mg/kg body weight to 8 cats was characterized by a mean (range) maximum concentration (Cmax) in plasma of approximately 165 (108-332) ng/mL. Cmax was achieved on average 0.32 (0.25-0.5) hours post-dosing (Tmax). Peak concentrations were followed by a decline in systemic exposure with a mean apparent elimination half-life (t½) of 16.8 (10.3-32.8) hours and mean area under the curve (AUC0-∞) of 3490 (1440-6760) hr*ng/mL. There appears to be an age-related effect on the pharmacokinetics of maropitant in cats with kittens (16 wks) having faster clearance than adults. The mean bioavailability of maropitant after subcutaneous administration in cats was 91.3%. The mean total body clearance (CL) and volume of distribution at steady-state (Vss) determined after intravenous administration at 0.25 mg/kg to 8 cats was 0.27 (0.14-0.59) L/h/kg and 3.04 (2.27 to 3.80) L/kg, respectively. Maropitant displays linear kinetics when administered subcutaneously within the 0.25 – 3 mg/kg dose range. Following repeated subcutaneous administration of once-daily doses of 1 mg/kg body weight for 5 consecutive days, accumulation was 250%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP1A and CYP3A-related enzymes were identified as the feline isoforms involved in the hepatic biotransformation of maropitant. Renal and fecal clearances are minor routes of elimination for maropitant, with less than 1% of a 1 mg/kg subcutaneous dose appearing in the urine or feces as maropitant. For the major metabolite, 10.4% of the maropitant dose was recovered in urine and 9.3% in feces. Plasma protein binding of maropitant in cats was estimated to be 99.1%.

EFFECTIVENESS:

DOGS

Prevention and Treatment of Acute Vomiting

In laboratory model studies, CERENIA Tablets dosed at a minimum of 2 mg/kg BW reduced the number of emetic events associated with established neural (central) and humoral (peripheral) stimuli. Following administration of apomorphine (central emetic stimuli), vomiting was observed in 33% (4 of 12) of Beagle dogs treated with CERENIA Tablets and 100% (12 of 12) of Beagle dogs treated with placebo tablets. Following administration of syrup of ipecac (peripheral emetic stimuli) vomiting was observed in 33% (4 of 12) of Beagle dogs treated with CERENIA Tablets and in 83% (10 of 12) of Beagle dogs treated with placebo tablets.

In laboratory model studies, CERENIA Injectable Solution administered at 1 mg/kg in Beagle dogs reduced the number of emetic events associated with established neural (central) and humoral (peripheral) stimuli. Following administration of apomorphine (central emetic stimuli), vomiting was observed in 16.7% (2 of 12) of dogs treated with CERENIA Injectable Solution and 83.3% (10 of 12) of placebo-treated dogs. Following administration of syrup of ipecac (peripheral emetic stimuli) vomiting was observed in 25% (3 of 12) of dogs treated with CERENIA Injectable Solution and in 100% (12 of 12) of dogs treated with placebo.

In a study of veterinary cancer patients, dogs were treated with CERENIA Injectable Solution or placebo either 1 hour prior to cisplatin (prevention) or after the first vomiting episode following cisplatin (treatment) and monitored for 5 hours. In the groups evaluated for prevention of vomiting, 94.9% (37/39) of the dogs administered CERENIA Injectable Solution and 4.9% (2/41) of the dogs administered placebo did not vomit. In the groups evaluated for treatment, 21% (8/38) of the dogs administered CERENIA Injectable Solution and 5.1% (2/39) of the dogs administered placebo had no further episodes of vomiting following treatment.

In a study of 275 canine patients presented to veterinary hospitals with a history of acute vomiting, dogs were initially administered CERENIA Injectable Solution or placebo on Day 0. Following the initial dose, dogs allocated to the CERENIA group were treated with either CERENIA Tablets at a minimum of 2 mg/kg orally or Injectable Solution at 1 mg/kg subcutaneously once daily at the discretion of the clinician. Dogs allocated to the placebo group were treated using either an injectable placebo solution or placebo tablets once daily at the discretion of the clinician. Of the 199 dogs included in the analysis for 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 CERENIA-treated group displayed vomiting during the study period.

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%
	CERENIA (145)	SC	145 (143*)	14	10%
Day 1	Placebo (45)	PO	22	3	14%
		SC	23	16	70%
	CERENIA (108)	PO	67	2	3%
		SC	41	16	39%
Day 2	Placebo (16)	PO	7	2	29%
		SC	9	6	67%
	CERENIA (37)	PO	24	0	0%
		SC	13	8	62%
Day 3	Placebo (6)	PO	2	0	0%
		SC	4	1	25%
	CERENIA (21)	PO	14	0	0%
		SC	7	5	71%
Day 4	Placebo (2)	PO	1	0	0%
		SC	1	1	100%
	CERENIA (7)	PO	5	0	0%
		SC	2	1	50%
Day 5	CERENIA (1)	SC	1	0	0%

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

In US field studies in veterinary patients, CERENIA Injectable Solution and Tablets were well tolerated in dogs presenting with various clinical conditions including parvovirus, gastroenteritis, and renal disease. There were no notable differences in mean laboratory values between CERENIA-treated and placebo-treated patients.

CERENIA Injectable Solution was used safely in dogs receiving other frequently used veterinary products such as fluid and electrolyte replacement solutions, antimicrobial agents, vaccines, antacids, and antiparasitic agents.

Prevention of Vomiting due to Motion Sickness

In a study of canine veterinary patients taken on a one-hour car journey and treated with either CERENIA Tablets at a minimum dose of 8 mg/kg BW or placebo tablets 2 hours prior to the journey, 67 of 122 (55%) of dogs vomited during the journey when treated with placebo while 8 of 122 (7%) vomited during the journey after treatment with CERENIA Tablets. The probability that a dog in this study, prone to motion sickness would NOT vomit during a journey if treated with CERENIA Tablets was 93%, while the probability was 48% if treated with placebo.

CATS:

In a field study, 195 cats were presented to veterinary hospitals with a history of vomiting associated with various clinical conditions including gastroenteritis, gastritis, pancreatitis, inflammatory bowel disease, neoplasia, and hepatic lipidosis. Cats were treated with CERENIA Injectable Solution or placebo (in a ratio of 2:1) and observed in the veterinary hospital for 24 hours for the presence of an emetic event(s) defined as the observation of the act of vomiting or the presence of vomitus. Cats could continue antiemetic treatment every 24 hours for up to 5 consecutive days at the discretion of the clinician. Of 165 cats included in the analysis for effectiveness, 2 CERENIA-treated cats (1.8%) vomited 1 time each and 10 placebo-treated cats (18.5%) vomited a total of 15 times in the first 24 hours post treatment.

Percent of Cats Vomiting for Each Study Day by Treatment

Study Day	Treatment	# cats	# vomited	% vomited
Day 0	Placebo	54	10	18.5
	CERENIA	111	2	1.8
Day 1	Placebo	20	4	20
	CERENIA	34	1	2.9
Day 2	Placebo	9	2	22.2
	CERENIA	8	0	0
Day 3	Placebo	5	0	0
	CERENIA	5	0	0
Day 4	Placebo	3	0	0
	CERENIA	1	0	0

ANIMAL SAFETY:

DOGS:

Laboratory and field studies have demonstrated that CERENIA Injectable Solution is well tolerated in dogs after subcutaneous administration.

Target Animal Safety Study for Acute Vomiting

Fifty six Beagle dogs (28 males and 28 females) approximately 16 weeks of age were administered CERENIA Injectable Solution subcutaneously once daily for 15 days at 0, 1, 3, and 5 mg/kg. There were 8 dogs (4 males and 4 females) in the 1 mg/kg group and 16 dogs (8 males and 8 females) in all other groups. The primary treatment-related findings were injection site reactions. Swelling, thickened skin, or pain at one or more of the injection sites on one or more days of the study were observed in 6 of 16 animals treated with 3 mg/kg/day and 5 of 16 animals treated with 5 mg/kg/day. Additionally, 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.

Beagle dogs approximately 8 weeks of age were administered CERENIA Injectable Solution subcutaneously once daily for 15 days at 0, 1, 3, and 5 mg/kg using a protocol similar to the previous study. A dose dependent increase in frequency and severity of bone marrow hypoplasia was observed histologically, One placebo-treated dog died on day 14 of the study and was diagnosed with suppurative pancreatitis and esophagitis. Interpretation of the study results is complicated by the health status of study animals. 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.

Beagle dogs approximately 10 weeks of age were administered either placebo tablets for 2 days, CERENIA Tablets at 8 mg/kg for 2 days, placebo (saline) subcutaneously (SC) for 5 days, CERENIA Injectable Solution at 1 mg/kg SC for 5 days, or CERENIA Tablets at 2 mg/kg for 5 days (8 dogs in each dose group). Mild pain associated with injection was noted in more dogs and lasted longer in dogs that received maropitant injections compared to saline. Males administered CERENIA at 8 mg/kg orally for 2 days had a decrease in food consumption. Body weight and food consumption were variable throughout the 4 week acclimatization period. Two dogs that received 8 mg/kg maropitant orally for 2 days were below the reference range for reticulocyte counts. Decreases in reticulocyte counts were also seen in 4 (of 8) placebo treated dogs (SC saline for 5 days). Hypocellular femoral bone marrow described as "minimal" was seen in 1 male that received 1 mg/kg maropitant SC for 5 days; reticulocyte counts were not available for this dog.

Target Animal Safety Study for Motion Sickness

Forty Beagle dogs (20 males and 20 females) between 16 - 18 weeks of age were administered CERENIA Tablets orally once daily for 6 days at 0, 8 and 24 mg/kg. There were 16 dogs (8 males and 8 females) in the 0 and 24 mg/kg groups and 8 dogs (4 males and 4 females) in the 8 mg/kg group. At 24 mg/kg, CERENIA Tablets caused decreases in food consumption, with decreases in body weight, liver and testis weight; and an increase in RBC count indicating hemoconcentration, but the effects on feed consumption, body weight, and RBCs did not persist in the post-treatment recovery period (beyond Day 5).

Beagle dogs approximately 8 weeks of age were administered CERENIA Tablets orally once daily for 6 days at 0, 8, and 24 mg/kg using a protocol similar to the previous study. One dog in the 24 mg/kg/day group died of unknown causes on study day 2 and a dose dependent increase in occurrence and severity of bone marrow hypoplasia and lymphoid depletion was observed histologically. Interpretation of these study results is complicated by the health status of study animals. 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.

Tolerance Study

Twenty four Beagle dogs (14 males and 10 females) between 11 and 25 weeks of age were administered CERENIA Tablets in 2 phases with 8 dogs per group. In the first phase the dogs were administered 0, 20 or 30 mg/kg orally once daily for 7 days and in the second phase 0, 40, or 50 mg/kg once daily for 7 days. CERENIA Tablets administered at 20 and 30 mg/kg caused occasional vomiting. CERENIA Tablets administered at 40 mg/kg and 50 mg/kg caused clinically relevant signs of weight loss, vomiting, soft stools, weakness, lethargy, salivation and hypokalemia. Additionally, leukopenia characterized by a neutropenia and a trend toward decreasing plasma phosphorus values was seen. Decreased heart rate and prolonged corrected QT intervals were seen in all treatment groups in a dose dependent manner.

CATS:

Thirty-two domestic short hair cats (16 males and 16 females) approximately 16 weeks of age were administered CERENIA Injectable Solution subcutaneously once daily for 15 days at 0, 1, 3, and 5 mg/kg. There were 8 cats (4 males and 4 females) in each group. Treatment-related, dose dependent findings included pain associated with injection of CERENIA and injection site heat, pain, redness, and firmness. Pain on injection was observed in 5% of cats at 0 mg/kg, 50% of cats at 1 mg/kg, and 75% of cats at 3 and 5 mg/kg. Injection site firmness >10 mm in diameter was observed at one or more of the injection sites, on one or more days of the study, in 1 of 8 cats at 1 mg/kg, 7 of 8 cats at 3 mg/kg, and 7 of 8 cats at 5 mg/kg. There was a statistically significant reduction (p=0.0171) in food intake at 5 mg/kg compared to cats at 0 mg/kg. One cat at 5 mg/kg was lethargic on Days 12, 13, and 14 of the study. Increased skin turgor was observed in 1 cat at 3 mg/kg on Days 10 and 11, 1 cat at 3 mg/kg on Day 12, and 1 cat at 5 mg/kg on Day 12. At gross necropsy, there were no treatment-related findings. Histopathologic evaluation of injection sites revealed a dose dependent inflammatory response.

STORAGE CONDITIONS:

CERENIA Tablets should be stored at controlled room temperature 20°-25°C (68°-77°F) with excursions between 15°-30°C (59°-86°F).

CERENIA Injectable Solution should be stored at controlled room temperature 20-25°C (68-77°F) with excursions between 15-30°C (59-86°F). After first vial puncture, CERENIA Injectable Solution should be stored at refrigerated temperature 2-8°C (36-46°F). Use within 90 days of first vial puncture. Stopper may be punctured a maximum of 25 times.

HOW SUPPLIED:

CERENIA peach-colored tablets are scored with a break line, and contain 16, 24, 60 or 160 mg of maropitant as maropitant citrate per tablet. 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.

CERENIA Injectable Solution is supplied in 20 mL amber glass vials. Each mL contains 10 mg of maropitant as maropitant citrate.

Made in France

NADA #141-262, Approved by FDA

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Distributed by: Pfizer Animal Health, Div. of Pfizer Inc, NY, NY 10017

Revised: May 2012

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NY, NY 10017