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CERENIA® INJECTABLE SOLUTION

Pfizer Animal Health

(maropitant citrate)

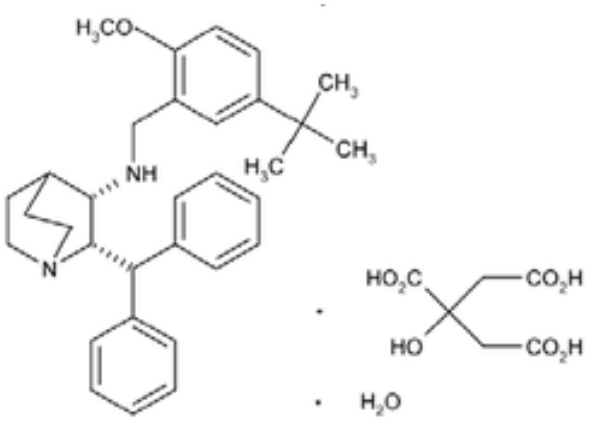
Antiemetic

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 $C_{32}H_{40}N_2O$ $C_6H_8O_7$ 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) 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: Administer CERENIA Injectable Solution subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 1 mL/kg (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.

CERENIA Injectable Solution is recommended for use in dogs 8 weeks and older and cats 16 weeks and older.

INFORMATION FOR USE: 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.

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

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

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: For subcutaneous injection only. 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:

For a complete listing of adverse reactions for CERENIA Injectable Solution 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.

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	4.0
Lethargy	1	2.4	2	2.6

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.

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

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 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.

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	0.0	3	2.3
Lethargy	0	0.0	2	1.5
Anorexia	0	0.0	1	0.8
Hematuria	0	0.0	1	0.8
Hypersalivation	0	0.0	1	0.8
Injection site swelling	1	1.6	0	0.0

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

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

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

The FDA Center for Veterinary Medicine has received reports of adverse events associated with the use of CERENIA in cats since its approval for dogs in 2007. 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 are listed in decreasing order of reporting frequency in cats: depression/lethargy, anorexia, injection site pain, and hypersalivation.

CLINICAL EXPERIENCE: 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 (NK_1) 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 $T_{1/2}$ 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 (C_{max}) in plasma of approximately 165 (108-332) ng/mL. C_{max} was achieved on average 0.32 (0.25-0.5) hours post-dosing (T_{max}). Peak concentrations were followed by a decline in systemic exposure with a mean apparent elimination half-life ($t_{1/2}$) of 16.8 (10.3-32.8) hours and mean area under the curve ($AUC_{0-\infty}$) 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:

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.

Frequency Distribution of Numbers of Vomiting Episodes For Treatment: Number of Vomiting Episodes Post Injection.

For Prevention: Total Number of Vomiting Episodes.

Number of Vomiting Episodes	Dogs with Vomiting Episodes* (% of Dogs)			
	Treatment of Vomiting		Prevention of Vomiting	
	Placebo (n=39**)	CERENIA (n=38**)	Placebo (n=41)	CERENIA (n=39)
0	2 (5.1)	8 (21.1)	2 (4.9)	37 (94.9)
1	3 (7.7)	7 (18.4)	2 (4.9)	1 (2.6)
2	4 (10.3)	6 (15.8)	3 (7.3)	1 (2.6)
3	3 (7.7)	6 (15.8)	4 (9.8)	0 (0)
4	4 (10.3)	4 (10.5)	3 (7.3)	0 (0)
5	2 (5.1)	5 (13.2)	4 (9.8)	0 (0)
6	14 (35.9)	1 (2.6)	1 (2.4)	0 (0)
7	2 (5.1)	1 (2.6)	12 (29.3)	0 (0)
8	2 (5.1)	0 (0)	5 (12.2)	0 (0)
9	2 (5.1)	0 (0)	2 (4.9)	0 (0)
10	0 (0)	0 (0)	2 (4.9)	0 (0)
11	1 (2.6)	0 (0)	0 (0)	0 (0)
12	NA	NA	1 (2.4)	0 (0)

*Dogs that exhibited an unacceptable level of vomiting (6 events) were withdrawn from the study and treated with another antiemetic.

**There were initially 41 and 42 dogs treated with either placebo or CERENIA Injectable Solution, respectively. However, if a dog did not vomit following cisplatin therapy, it did not receive a post-cisplatin treatment with either placebo or CERENIA, and hence it was not considered in the therapeutic evaluation.

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.

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, Based Upon Treatment and Route of Administration.

Study Day	Treatment	# cats	# vomited	% vomited
Day 0	Placebo	54	10	18.5
	CERENIA	111	2	1.8
Day 1	Placebo	20	4	20.0
	CERENIA	34	1	2.9
Day 2	Placebo	9	2	22.2

	CERENIA	8	0	0.0
Day 3	Placebo	5	0	0.0
	CERENIA	5	0	0.0
Day 4	Placebo	3	0	0.0
	CERENIA	1	0	0.0

ANIMAL SAFETY:

DOGS:

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

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.

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

NADA #141-263, Approved by FDA

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

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Made in France

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