

# Cerenia™

(maropitant citrate)

## Injectable Solution

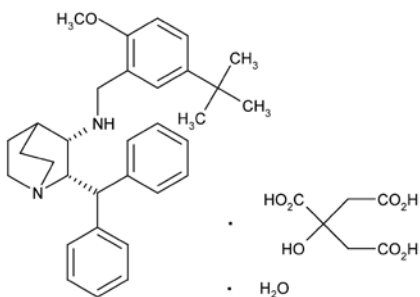
### Antiemetic

For subcutaneous injection in dogs only

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

**DESCRIPTION:** Maropitant is a neurokinin (NK<sub>1</sub>) 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<sub>32</sub>H<sub>40</sub>N<sub>2</sub>O C<sub>6</sub>H<sub>8</sub>O<sub>7</sub> H<sub>2</sub>O 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.

**DOSE AND ADMINISTRATION:** Administer CERENIA Injectable Solution subcutaneously at 1.0 mg/kg (0.45 mg/lb) equal to 1.0 mL/10 kg (1.0 mL/22 lb) of body weight once daily for up to 5 consecutive days.

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

| Dog body weight |             | Dose Volume (mL) |
|-----------------|-------------|------------------|
| Pounds          | Kilograms   |                  |
| 2.2             | 1.0         | 0.10             |
| 2.3 – 4.4       | 1.1 – 2.0   | 0.20             |
| 4.5 – 6.6       | 2.1 – 3.0   | 0.30             |
| 6.7 – 8.8       | 3.1 – 4.0   | 0.40             |
| 8.9 – 11.0      | 4.1 – 5.0   | 0.50             |
| 11.1 – 16.5     | 5.1 – 7.5   | 0.75             |
| 16.6 – 22.0     | 7.6 – 10.0  | 1.00             |
| 22.1 – 33.0     | 10.1 – 15.0 | 1.50             |
| 33.1 – 44.0     | 15.1 – 20.0 | 2.00             |
| 44.1 – 66.0     | 20.1 – 30.0 | 3.00             |
| 66.1 – 88.0     | 30.1 – 40.0 | 4.00             |
| 88.1 – 110.0    | 40.1 – 50.0 | 5.00             |
| 110.1 – 132.0   | 50.1 – 60.0 | 6.00             |

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 hypoplasia was seen at higher frequency and greater severity in puppies treated with CERENIA than in control puppies. In puppies 16 weeks and older, bone marrow hypoplasia was not seen (See Animal Safety Section).

**PRECAUTIONS:** For subcutaneous injection only. The safe use of CERENIA has not been evaluated in dogs used for breeding, pregnant or lactating bitches, dogs with gastrointestinal obstruction, or dogs that have ingested toxins. Use with caution in dogs with hepatic dysfunction. 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. Commonly used protein bound drugs include NSAIDs, cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of CERENIA has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

**ADVERSE REACTIONS:** 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 1.0 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 1.0 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               | 1.0     |
| 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     |

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.

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 PHARMACOLOGY:

#### Pharmacokinetics

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 <sub>0-inf</sub> (hr*ng/mL) | 860±137   | 561±322             | 7840±5600           |
| C <sub>max</sub> (ng/mL)        | 92±34   | 81±32               | 776±604             |
| T <sub>1/2</sub> (hr)           | 8.84 (6.07–17.7)  | 4.03 (2.48–7.09)    | 5.46 (3.39–7.65)    |
| T <sub>max</sub> (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<sub>1/2</sub> 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%).

#### 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 cerebro-spinal fluid. Maropitant is a neurokinin 1 (NK<sub>1</sub>) 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.<sup>1</sup> 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.

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

**EFFECTIVENESS:** 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*<br>(% of Dogs) |                       |                        |                     |
|-----------------------------|---|-----------------------|------------------------|---------------------|
|                             | Treatment of Vomiting                       |                       | Prevention of Vomiting |                     |
|                             | Placebo<br>(n = 39**)                       | CERENIA<br>(n = 38**) | Placebo<br>(n = 41)    | CERENIA<br>(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.

**ANIMAL SAFETY:** 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 was 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.

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.

**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). Use within 28 days of first vial puncture.

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

US Patents: See US 6,222,038; US 6,255,320

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