

# Rethinking Perioperative Vomiting In Dogs



## Advisory Board



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Reviewed and Supported by:



# Introduction

In April 2019, an expert panel was assembled to discuss the future of perioperative antiemetics, with the intent of developing a set of best practice recommendations and implementation strategies. The goal was to elevate the level of care for patients concerning postoperative vomiting, return to feeding, and recovery quality. Within this discussion, the board also addressed the advantages that this approach holds for the healthcare team, practice, and pet owners. The implementation strategies shared by the board cover both logistical tips as well as communication guidelines for sharing this information with your team and pet owners.

## Parallels between Anesthesia and Antiemetics

Before 1960 there were no recognized veterinary anesthesiologists in North America, and anesthesia in veterinary procedures continued to be used sparingly into the 1970s. At one point, it was even thought that “The induction of veterinary anesthesia was delayed by the misperception that the induction of anesthesia in animals was painful—and unnecessary—one needed but to hobble the animal.”<sup>1</sup> Parallels exist between the history of analgesia in pets and the current research being done into perioperative emesis, with the future of antiemetics aimed at improving care of surgical patients. Dr. Ralph Harvey speaks enthusiastically about the parallel, stating that both medical advances represent similar rejuvenations of patient care models. Other members of the board in this space echo his thoughts:

*“I think of it as how we (veterinarians) thought about pain management 20–30 years ago in that ‘animals don’t feel pain the way people do’...now that sentiment has been dispensed with and pain management is at the forefront of good patient care. I think that we are evolving in the same way with respect to perianesthetic vomiting and nausea.” Dr. Bonnie Kraus*

## Brief overview of Opioid use

Opioids have been a critical component of preanesthetic protocols:

- Excellent analgesia
- Good level of sedation
- No negative hemodynamic consequences
- Inhalant sparing, reducing the risk of hypotension
- Particularly useful for geriatric and cardiac patients
- Reversible effects
- Wide variety of options within the field for flexible protocols

The board shared the opinion that, even with the current focus on ‘opioid-sparing’ anesthesia protocols, opioids still have an important place in balanced veterinary anesthesia protocols. It was stated that opioids as a class of medicine are fairly benign, **except for vomiting as a significant side effect.**

## The importance of a good recovery

A gradual, successful recovery after surgery has benefits that extend beyond the patient to the pet owner, the clinic team, and the practice itself. These benefits are discussed in more detail in the following section.

But first, what are the characteristics of a successful recovery and what factors influence your likelihood to achieve them?

The members of the advisory board identified 3 key areas that help create goals for what they consider an ideal recovery:

- **A gradual, calm transition to wakefulness with no vomiting**

- Awake and responsive in the clinic with good homeostasis
- Ambulatory upon discharge and rapid return to feeding

Following that, 3 strategies were discussed that particularly influence these success indicators:

- Appropriate and balanced analgesia
- Sedation to help in the transition to wakefulness after the procedure
- Use of Cerenia (maropitant citrate) perioperatively to hasten the **return to normal feeding** upon recovery.<sup>6</sup>



***“Veterinarians have long pledged ourselves to the relief of suffering. The earlier big target was pain relief, and we achieved that part of the goal with a significant unfortunate trade-off of increased suffering associated with vomiting. Now we have both the knowledge and the tools to counteract and relieve the suffering of vomiting as well.” Dr. Ralph Harvey***

## **How is Perioperative vomiting affecting your practice?**

- Aspiration pneumonia
- Delayed return to feeding
- Practice health
- Clinic team satisfaction
- Quality of life

## **Aspiration pneumonia**

From a medical perspective, perianesthetic vomiting can be an extremely negative side effect because of the rare, but highly fatal, risk of aspiration pneumonia.

Several of the experts who were assembled shared experiences that they’d had with aspiration pneumonia, demonstrating the lasting effects that a serious complication during a routine surgery can have.

***“It’s catastrophic when aspiration pneumonia happens. Even if it’s not very common, it’s still worth preventing.” Dr. Tamara Grubb***

Dr. Bonnie Kraus was driven to investigate the literature on this complication further and found that vomiting was frequently associated as a complicating factor.

While the incidence of vomiting during surgery varies depending on the anesthetic type, dose, and administration, the advisory board felt strongly that the risk of perianesthetic vomiting was unacceptable and warranted the administration of a preanesthetic antiemetic in every procedure.



## Delayed return to feeding

Delayed return to feeding after a surgical procedure can have an array of effects on the patient and pet owner. Below are some of the benefits of returning to feeding that were discussed by the board:

### Medical

- Return to normal gut function; maintain gastrointestinal (GI) integrity
- Maintenance of a healthy microbiome/reduction in risk of bacterial translocation
- Support for the immune system
- Positive nitrogen balance for restoring blood sugar
- Return to feeding for diabetic and pediatric patients as soon as they are alert enough to eat

### Animal Welfare

- Return to normal feeding is an indicator of lack of pain, fear (maladaptive stress response), anxiety, and nausea

### Pet owner peace of mind and satisfaction

- Pet owners interpret normal feeding as happiness and quality of life in their pet
- Lack of eating can be interpreted by the owner as “anger” toward them; it fractures the human-animal bond
- The multi-pet household goes back to normal
- Drives the perception of good quality of care and strengthens the bond with the hospital and veterinary team

***“I deal with nausea and inappetence on a daily basis, and we know how inappetence and not eating are tied to quality of life...owners associate feeding their pets with health and love.” Dr. Sue Ettinger***

### GI Function

Prolonged periods of fasting in dogs have been shown to alter the species and diversity of bacteria present in the GI microbiota.<sup>3</sup> Dr. Ralph Harvey highlighted the effects of an imbalanced microbiota, particularly relating to its relationship with the immune system. Dr. David Twedt agreed, providing more detail into the factors that are involved:

***“Not eating changes the bacterial flora, you have greater risk for translocation of bacteria, endotoxins, GI integrity. So yeah, that’s the big thing now in GI is this dysbiosis or imbalance of the microbiome...getting animals to eat is very important.” Dr. David Twedt***

### Pet Owner Experience

Inappetence may impact the human-animal bond: In the experience of the advisory board veterinarians, pet owners tended to view a dog rejecting food after surgery as a rejection of the pet owners themselves, leading to pet owner guilt.

Dr. Ralph Harvey also asserted that pet owners think that food is love and a delayed return to feeding fractures the bond between pet and owner. It was further suggested by Dr. Tamara Grubb that a pet owner is likely to anthropomorphize his/her pet and draw the conclusion that the pet is in fact mad at the owner over the surgery.

Following this, she paraphrased her pet owner’s typical perspective: “When they eat, I know they’re happy...and everything’s going to be OK.”



In a study, of the 12 dogs that returned to feeding by 6 hours into recovery, 4/12 (33.3%) had received placebo treatment and 8/12 (66.7%) had been treated with Cerenia pre-operatively. Seven of 13 placebo-treated dogs (53.8%) had not eaten at least 100 grams of food 20 hours after surgery while only one Cerenia-treated dog (6.7%) still had not eaten a total of 100 grams of food at 20 hours.

## Practice health

The experience of the pet owner was discussed hand in hand with the perception of the veterinary clinic, since a positive pet owner experience is good for the health of the practice. The primary insight discussed was the concept of value: A pet owner who is happy with his/her pet's surgery will see the value of the clinic's services, which is what drives pet owner willingness to pay:

*“People will pay for value. And we want value-added experiences, options & standards of care in our hospitals.” Dr. Ralph Harvey*

This was a wide consensus among the board, as members agreed that a pet and owner who share a stronger bond on discharge are happier with the clinic and more likely to be loyal customers in the future.

Practice operation costs can also improve due to the need for fewer team members and less overhead being tied up by surgical complications, extra patient holding time, repeated visits or therapy, phone calls regarding the dog not eating, and challenging pain management.

## Clinic team satisfaction

Patients vomiting after surgery or complications during surgery can be profoundly damaging to the well-being and peace of mind of the healthcare team. The clinic team carries this stress and guilt into their personal lives, and it can lead to conflict amongst the team, long-term job dissatisfaction, and employee turnover.

On top of directly dealing with surgical complications and clean-up duties, the healthcare team also values their bond with the owner. Dr. Sue Ettinger related the improvement of team mental health to the reduction of aggravated phone calls and emails from pet owners to her staff.

*“Absolutely, it lowers stress for your healthcare team. It lowers the incidence of bites and scratches. And those are, in part, some of the benefits that are seen with Fear Free approaches.” Dr. Ralph Harvey*

## Quality of life

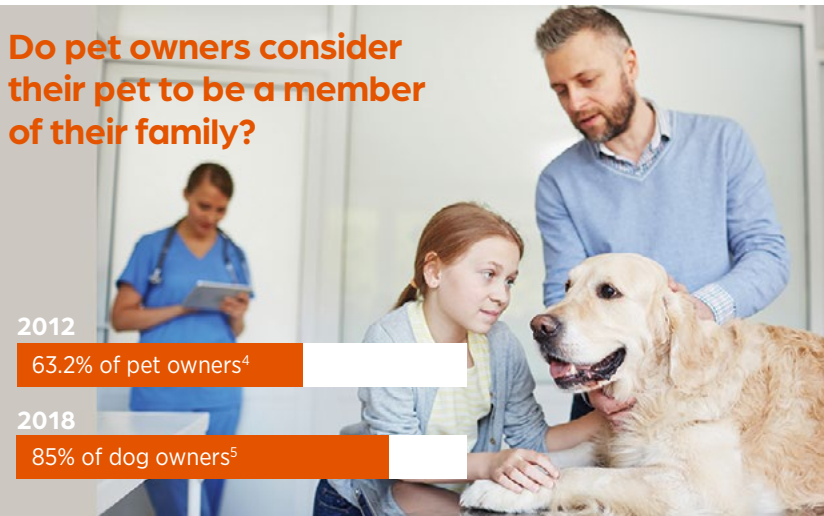
Ultimately, improvements to surgical routines relate back to the importance of the patient's quality of life and how it is impacted by perioperative discomfort, anxiety, and pain.

**What does it mean to prioritize the patient's quality of life in a clinic protocol?** Consider the perspective of the dog owner. Among pet owners, 63.2%<sup>4</sup> considered their pets to be family members. Another 35.8 % considered their pets to be pets or companions. The remaining 1% considered their pets to be property, and that feeling is trending upward.

In 2018, that percentage climbed all the way to 85% of dog owners.<sup>5</sup> This means that the large majority of dog owners are likely valuing pros and cons of their dog's surgery in the same way they would evaluate a procedure involving any other family member.

*“Happier pets, happier clients, a happier team.” Dr. Sue Ettinger*

The advisory board participants were passionate about changing the perspective about canine vomiting as a minor occurrence, when in fact it contributes to misery and suffering, leading to fear, anxiety, and stress for the dog. Prevention has a positive impact on quality of life for the dog, the healthcare team, and the owner.





## Common perceptions & current insights

### Perception #1

Vomiting in dog is “normal” and not distressing to the dog

While dogs seem to easily vomit (and often eat) stomach contents, “nausea” is subjective. Since dogs are a non-verbal species, we need to use that term knowing that they can’t tell us what they are feeling. Dogs that vomit on the way to the veterinary hospital for an operation (motion sickness and/or anxiety), and that vomit at the hospital or after a procedure, are very likely experiencing some degree of discomfort and fear.

*“So I presume that our animals who come to us, who have nausea as a result of motion sickness or as a result of our premeds, are suffering from that same bad feeling for a long period of time.” Dr. Ralph Harvey*

### Perception #2

Preanesthetic vomiting in dogs is desirable to ensure the stomach is empty and thus reduce the risk of aspiration

Despite perceptions, vomiting is not an effective tactic to empty the stomach.

*“In the early days of our anesthesia training, we thought if animals vomited preoperatively, their stomach would be empty and that, that might even be a benefit. And yet we saw many patients who would vomit repeatedly showing, demonstrating for us that the vomiting did not necessarily empty their stomach.” Dr. Ralph Harvey*

### Perception #3

Patients suspected of having a foreign body should not receive Cerenia®

When an obstruction or foreign body is suspected, use antiemetic therapy conservatively while continuing to test for obstruction.

*Dr. David Twedt’s experience with patients’ suffering from GI obstructions found that Cerenia “stops dogs that have obstructions from vomiting, and it has really been shown not to have major effects on increasing or decreasing GI motility.”*

## How to get patients back on their paws faster

A study performed at Colorado State University with Dr. David Twedt's research team found that canine patients given a dose of Cerenia® preanesthetically were more likely to eat within 3 hours after extubation than patients dosed with morphine preanesthetically. 64.7% of dogs given Cerenia returned to eating within 3 hours, compared to only 15.3% of patients with morphine.<sup>6</sup>

The results are in line with recent research on the use of Cerenia, which found that it significantly reduced vomiting in dogs that were premedicated with morphine. This study further reported that the use of Cerenia improved the quality of recovery (as measured by decreased aimless movements, vocalization, and panting) compared to placebo-treated dogs.<sup>2</sup>

*"I think it's really important that we educate pet owners and educate veterinarians about the importance of return to normal eating and how an antiemetic can get their pets eating sooner. Again, I think there are always two audiences to educate because it makes the vet's job so much easier when the pet owners want it."*

*Dr. Sue Ettinger*

Cerenia has also been adopted by Dr. Harvey and his colleagues from the teaching hospital at University of Tennessee College of Veterinary Medicine. He attributed the school-wide adoption of adding an antiemetic to the anesthetic protocol to a better understanding around the reduction of fear, anxiety and stress in their patients, and getting them to eat sooner post-surgery.

## What can we learn from human health studies?

An article published in March 2019 investigated the incidence of postdischarge nausea and vomiting (PDNV) in humans and found that these figures were underreported; the actual number of surgical patients who suffer from PDNV is much higher than they originally thought.<sup>7</sup>

Similarly, Dr. Ralph Harvey referenced a body of work in human medicine that compared the cost of antiemetic medications with the cost of complications such as an episode of aspiration or delayed recovery, which found that these overhead costs were quite high.<sup>8</sup>

A consensus guideline printed for human postoperative nausea and vomiting management reports that human patients identify nausea and vomiting as one of the most dreaded postoperative consequences, often ranking it above pain. The guidelines specify the need to move toward the use of evidence-based prophylactic treatment, highlighting the importance of prevention of these symptoms as opposed to reactionary medicine.<sup>9</sup>

It is possible that dogs experience nausea in the same way that people do: Dr. Harvey tends to presume that animals presenting with vomiting due to motion sickness or perioperative medication experience negative feelings of nausea over a long period of time. However, it is impossible to say for sure because it is a nonmeasurable subjective experience. Therefore, veterinarians and veterinary antiemetics tend to focus on perioperative vomiting compared to the human discussion of preoperative nausea and vomiting (PONV) and PDNV.

*"I see that people are really concerned about nausea and vomiting. But I see that they're equally concerned about their animals...and they're willing to pay the same amount to relieve that." Dr. David Twedt*

## Looking through the eyes of the pet owner

Recall the AVMA statistics concerning pet owners' relationships with their pets: 85% of dog owners consider them as family members.<sup>5</sup> In the same way that they wouldn't consider the cost of a family member's surgery, they often have other prominent values when approaching veterinary care.

Dr. Ralph Harvey describes the power of value-added care, a philosophy of providing care that emphasizes enriching and improving the patient experience, focusing not on the cost that is being charged, but the value that is being provided. It all starts with having the conversation with pet owners and educating them about the services provided.

***"I think for veterinarians, some of the perceived barriers to antiemetic treatment are the cost and the time involved in waiting for the treatment to work effectively, which can take up to 1 hour - surveys of dog owners have indicated that they are willing to spend the necessary time and also pay for antiemetic treatment for their pet: They value the care of their pet more than the time or cost associated with this side effect of anesthesia." Dr. Bonnie Kraus***

In a survey of 897 pet owners 84% of them would be concerned if their pet vomited when they got home from surgery, and 59% said that they would be extremely concerned.<sup>10</sup>

**If your veterinarian offered a treatment to prevent your dog from vomiting, how likely would you be to buy it, and how much would you pay?** On average, pet owners indicated that they would be willing to pay \$74 for this treatment.<sup>10</sup>

- If their vet offered treatment to help prevent their dog from vomiting after surgery, 58% (n=521) of dog owners 3 say they would be extremely/very likely to buy it.<sup>10</sup>

***"We first started seeing this with better pain management. When people would say, "Wow! My dog did so much better this time than last time," it was pain management then and now it's more antiemetics, but you're absolutely right, they notice that. It is important." Dr. Tamara Grubb***

## Board Recommendations for Best Practice

1. Use of an antiemetic in canine general anesthesia is best practice, even without opioids.
2. Change our thinking about emesis: Centrally driven emesis is normal; peripherally driven is not. It is aversive and destructive.
3. Change our mindset to a preventive/proactive one to avoid discomfort and distress.
4. Focus on return to normal feeding as much as on emesis: the importance of eating on gut function, immune function, and the microbiome.
5. Relieve FAS – fear, anxiety, stress and improve quality of life.

***"When we were trying to get people to do pain management, they would ask the clients if they were willing to pay for pain management. And I think most veterinarians found that the owners were absolutely willing to pay for it, and I think maybe treatment of peri-anesthetic vomiting & nausea goes the same way...in that you ask owners if they would be willing to pay for anti-emetic treatment...we have found that >90% are concerned about their dog experiencing nausea & vomiting associated with anesthesia and are willing to pay for treatment to avoid this side effect in their pet." Dr. Bonnie Kraus***

***"For me, I have gotten to the point where I have added Cerenia® as part of the anesthesia protocol in my oncology practice. While I also use Cerenia commonly in my chemotherapy patients as a preventative and to treat emesis, I have just made it part of my anesthetic protocol in general." Dr. Sue Ettinger***





## Happier pets, happier clients, a happier team: path to best practice

Talking about the importance of controlling perioperative vomiting is one thing, but the board recognized that the challenge is in the implementation. They shared some of their own best practices as to how they were able to incorporate this routine into their busy practices:

- Include antiemetic as a default cost, built into the package for most surgeries. Dr. Bonnie Kraus: ***“We don’t ask clients if they want pain management; we provide pain management, and that’s become the standard of care.”***
- Speak with pet owners in a way that communicates the value of your services. This includes educating pet owners about the potential incidence of nausea, as well as educating around the broad effects of delayed return to feeding and how an antiemetic can improve it. Additionally, this means educating your team on how best to collect patient information. Dr. Sue Ettinger: ***“It’s the nurses who are going in, in many situations, or the students or whoever we’re training, and asking, ‘How’s the appetite?’ That’s not the right question, because the pet owner might say good when they are only getting the pet to eat homecooked food and not their regular food. A better question is: what are they eating? Whether it’s after chemo, anesthesia or the recovery period afterwards, we must help the owner identify a decreased or poor appetite so we can treat it accordingly.”***
- When possible, avoid guessing about what educated pet owners want to pay for in the course of their pet’s surgery: The board members use Cerenia® routinely in most surgeries because their pet owners find it to be a positive value-add.
- In the event that a pet owner needs to discuss lower cost options, or for non-income-generating surgeries such as some spays and neuters, consider ways to offer 2 tiers of treatment while still advocating for and educating about the inclusion of a base level of antiemetic dosing in every protocol.
- Involve the whole clinic team in developing new surgical routines. Administering antiemetics means less vomit for the healthcare team to clean up and more happy patients. With whole clinic buy-in, we see whole clinic benefit. The ad board members discussed the importance of everyone taking part, and Dr. Sue Ettinger shared her thoughts on her nursing team: ***“That’s how programs are successful: You have to have the team. The whole team, it’s not just the doctors; it’s the nurses as well... I think that’s how you make protocol successful.”***
- Have a team member arrive at the clinic an hour early to accept surgical patients and administer subcutaneous antiemetic in preparation for surgery. If timing is a concern? Dr. Bonnie Kraus: ***“We know that the clients have no problem waiting, coming in early, an extra hour... so if they had all their surgery animals dropped off with one technical staff there, and could dose them in the morning.”***
- Consider alternative routes of administration if it is not possible to have the antiemetic treatment given an hour before surgery.

***“I think it’s just habit that says we can’t do it.” Dr. Tammy Grubb***

# Cerenia®

(maropitant citrate)

## Tablets and Injectable Solution

### Antiemetic

CERENIA Tablets

For oral use in dogs only

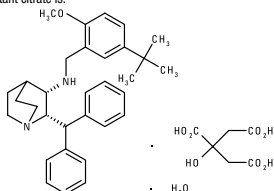
CERENIA Injectable

For subcutaneous or intravenous injection in dogs and cats

**CAUTION:** Federal 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>23</sub>H<sub>26</sub>N<sub>2</sub>O C<sub>6</sub>H<sub>5</sub>O<sub>2</sub>, H<sub>2</sub>O and the molecular weight 678.81. The chemical name is (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate. Each peach-colored oval tablet is scored and contains 16, 24, 60 or 160 mg of maropitant as maropitant citrate per tablet. 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.

### DOSE AND ADMINISTRATION:

#### For Prevention of Acute Vomiting (CERENIA Tablets)

**For Prevention of Acute Vomiting in dogs 2-7 months of age:** 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 (see WARNINGS and Animal Safety).

**For Prevention of Acute Vomiting in dogs 7 months of age and older:** Administer CERENIA Tablets orally at a minimum dose of 2 mg/kg (0.9 mg/lb) body weight once daily until resolution of acute vomiting.

If vomiting persists despite treatment, the case should be re-evaluated. CERENIA is most effective in preventing acute vomiting associated with chemotherapy if administered prior to the chemotherapeutic agent.

**For prevention of acute vomiting, dispense whole or half tablets in strength(s) that most closely result in a 2 mg/kg dose:**

| Dog body weight |           | Number of Tablets |       |       |
|-----------------|-----------|-------------------|-------|-------|
| Pounds          | Kilograms | 16 mg             | 24 mg | 60 mg |
| 8               | 4         | 1/2               |       |       |
| 15              | 8         | 1                 |       |       |
| 25              | 12        |                   | 1     |       |
| 50              | 24        |                   | 2     |       |
| 65              | 30        |                   |       | 1     |
| 130             | 60        |                   |       | 2     |

#### Interchangeable use with CERENIA Injectable Solution for Prevention of Acute Vomiting:

In dogs that are actively vomiting, to ensure that the full initial dose is administered, CERENIA Injectable Solution is recommended at a dose of 1 mg/kg once daily. Thereafter, for the prevention of acute vomiting, CERENIA Tablets at a dose of 2 mg/kg once daily may be used interchangeably with CERENIA Injectable Solution for up to 5 days.

#### For Prevention of Vomiting Due to Motion Sickness in dogs 4 months and older (CERENIA Tablets)

**For Prevention of Vomiting due to motion sickness in dogs 4 months of age 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 (see WARNINGS and Animal Safety).

Administer CERENIA Tablets a minimum of two hours prior to travel with a small amount of food to mitigate vomiting associated with administration of the dose on an empty stomach; however, refrain from feeding a full meal prior to travel.

#### Prevention of Vomiting Due to Motion Sickness in Dogs 4 months of age and older:

**Dispense whole or half tablets in strengths that most closely result in an 8 mg/kg dose once daily for up to 2 consecutive days:**

| Dog body weight |           | Number of Tablets |       |       |        |
|-----------------|-----------|-------------------|-------|-------|--------|
| Pounds          | Kilograms | 16 mg             | 24 mg | 60 mg | 160 mg |
| 2               | 1         | 1/2               |       |       |        |
| 3               | 1.5       |                   | 1/2   |       |        |
| 4               | 2         | 1                 |       |       |        |
| 6               | 3         |                   | 1     |       |        |
| 8               | 4         | 2                 |       |       |        |
| 13              | 6         |                   | 2     |       |        |
| 16              | 7.5       |                   |       | 1     |        |
| 22              | 10        |                   |       |       | 1/2    |
| 33              | 15        |                   |       | 2     |        |
| 44              | 20        |                   |       |       | 1      |
| 66              | 30        |                   |       |       | 1 1/2  |
| 88              | 40        |                   |       |       | 2      |
| 132             | 60        |                   |       |       | 3      |

CERENIA Injectable Solution should not be used interchangeably with CERENIA Tablets for the prevention of vomiting due to motion sickness (8mg/kg).

#### For Prevention and Treatment of Acute Vomiting in Dogs (CERENIA Injectable):

**Dogs 2-4 Months of Age:** Administer CERENIA Injectable Solution subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 0.1 mL/kg (0.1 mL/2.2 lb) of body weight once daily for up to 5 consecutive days.

**Dogs 4 months of Age and Older:** Administer CERENIA Injectable Solution intravenously over 1-2 minutes or subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 0.1 mL/kg (0.1 mL/2.2 lb) of body weight once daily for up to 5 consecutive days.

In dogs that are actively vomiting, it is recommended to initiate treatment with CERENIA Injectable Solution. Thereafter, CERENIA Tablets may be used for the prevention of acute vomiting at 2 mg/kg once daily. (See CERENIA Tablets package insert for complete prescribing information).

**For Prevention of Vomiting in Dogs 4 months of Age and Older Caused by Emetogenic Medications or Chemotherapeutic Agents:** Administer CERENIA Injectable Solution intravenously over 1-2 minutes or subcutaneously at 1 mg/kg (0.45 mg/lb) of body weight one time, 45-60 minutes prior to use of emetogenic medications or chemotherapeutic agents.

#### For Treatment of Vomiting in Cats 4 Months of Age and Older (CERENIA Injectable):

Administer CERENIA Injectable Solution intravenously over 1-2 minutes or subcutaneously at 1 mg/kg (0.45 mg/lb) equal to 0.1 mL/kg (0.1 mL/2.2 lb) of body weight once daily for up to 5 consecutive days.

The underlying cause of acute vomiting should be identified and addressed in dogs and cats that receive CERENIA Injectable Solution. If vomiting persists despite treatment, the case should be re-evaluated.

**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 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.

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

Use with caution in patients with hepatic dysfunction because CERENIA Injectable Solution is metabolized by CYP3A, CYP2D15 (dogs) and CYP1A (cats) enzymes (see Pharmacokinetics). The influence of concomitant drugs that may inhibit the metabolism of CERENIA Injectable Solution has not been evaluated. CERENIA Injectable Solution is highly protein bound. Use with caution with other medications that are highly protein bound. The concomitant use of CERENIA Injectable Solution 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. Drug compatibility should be monitored in patients requiring adjunctive therapy.

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

The safe use of CERENIA Injectable Solution has not been evaluated in dogs or cats used for breeding, or in pregnant or lactating bitches or queens.

### ADVERSE REACTIONS:

#### Prevention of Acute Vomiting (minimum of 2 mg/kg) (CERENIA Tablets)

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

#### Frequency of Adverse Reactions by Treatment

| Adverse Reaction          | Placebo (n=69) |              | CERENIA (n=206) |              |
|---------------------------|----------------|--------------|-----------------|--------------|
|                           | # dogs         | % occurrence | # dogs          | % occurrence |
| 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.

#### Prevention of Vomiting Due to Motion Sickness (minimum of 8 mg/kg) (CERENIA Tablets)

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 once daily. 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 <sup>1</sup> | 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          |

<sup>1</sup> 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            |

The following Adverse Reactions were reported during the conduct of a US clinical field trial where CERENIA Tablets were administered once daily for 28 consecutive days to 32 dogs: lethargy, vomiting, inappetence, corneal edema, and enlarged lymph nodes.

#### Post-Approval Experience (CERENIA Tablets - Revised May 2019)

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 reported for dogs are listed in decreasing order of frequency: anorexia, depression/lethargy, hypersalivation, vomiting, diarrhea, trembling, ataxia, allergic reactions, weight loss, convulsion, hyperactivity, and panting.

Cases of ineffectiveness have been reported.

Cases of death (including euthanasia) have been reported.

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Zoetis Inc. at 1-888-963-8471 or [www.zoetis.com](http://www.zoetis.com).

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

#### (CERENIA Injectable):

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

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 Zoetis Inc. at 1-888-963-8471.

### 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     |

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 (Rev. 2015 CERENIA Injectable Solution)

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 reported for dogs are listed in decreasing order of reporting frequency for CERENIA Injectable Solution: Pain/vocalization upon injection, depression/lethargy, anorexia, anaphylaxis/anaphylactoid reactions (including swelling of the head/face), ataxia, convulsions, hypersalivation, tremors, fever, dyspnea, collapse/loss of consciousness, recumbency, injection site reactions (swelling, inflammation) and sedation. 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 <sup>1,2</sup>    | 1              | 1.6     | 30              | 22.6    |
| Significant Response to Injection <sup>1,3</sup> | 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       |

<sup>1</sup> The clinician observed and graded each cat's response to injection.

<sup>2</sup> Cat objected to the injection by retreating and vocalizing

<sup>3</sup> Cat objected to the injection by retreating, hissing, scratching, and vocalization

### Post-Approval Experience (Rev. 2015 CERENIA Injectable Solution)

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 reported for cats are listed in decreasing order of reporting frequency for CERENIA Injectable Solution: Depression/lethargy, anorexia, hypersalivation, pain/vocalization upon injection, dyspnea, ataxia, fever, recumbency, vomiting, panting, convulsion, and muscle tremor. Cases of death (including euthanasia) have been reported.

**CLINICAL EXPERIENCE (CERENIA Injectable):** The pain or vocalization upon injection resolves within minutes without treatment. Administration of CERENIA Injectable Solution at refrigerated temperature may mitigate this response (see **DOSE 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 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, and syrup of ipecac.

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

#### Pharmacokinetics (CERENIA Tablets)

Mean (±SD) Plasma Pharmacokinetic Parameters for Maropitant in Beagle Dogs after single dose and repeat oral doses of Maropitant:

| PK Parameter                                       | 2 mg/kg Single Dose | 2 mg/kg repeat Doses <sup>1</sup> | 8 mg/kg Single Dose | 8 mg/kg repeat Doses <sup>1</sup> |
|--|---------------------|-----------------------------------|---------------------|-----------------------------------|
| T <sub>max</sub> <sup>2</sup> (hr)                 | 2.0 (1.5 - 3.0)     | 1.5 (1.0 - 3.0)                   | 1.5 (1.0 - 3.0)     | 2.5 (1.5 - 7.0)                   |
| C <sub>max</sub> (ng/mL)                           | 154 (111)           | 304 (165)                         | 588 (416)           | 1409 (616)                        |
| AUC <sub>0-24</sub> (ng*hr/mL)                     | 1440 (982)          | 3890 (3030)                       | 6730 (5030)         | 26600 (9200)                      |
| T <sub>1/2</sub> <sup>2</sup> (hr)                 | NC                  | 7.69 (6.21 - 17.8)                | NC                  | 25.4 (6.06 - 30.0)                |
| Accumulation Ratio (R <sub>ss</sub> ) <sup>3</sup> | NA                  | 2.46 (1.68, 3.61)                 | NA                  | 4.81 (3.28, 7.05)                 |

<sup>1</sup>Following once daily doses of maropitant for 14 days.

<sup>2</sup>Median (Range)

<sup>3</sup>Ratio=Multiple Dose AUC<sub>(0-24)</sub>/Single Dose AUC<sub>(0-24)</sub>. Least square means (95% Confidence Interval)

NA= Not Applicable

NC= Not Calculated

Following oral administration, median time to reach C<sub>max</sub> was within 2.5 hr. The absolute bioavailability of maropitant was low (24%) following oral administration of 2 mg/kg maropitant. 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). However as doses increase (20-50 mg/kg PO), the 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. Due to dose dependent pharmacokinetics, the maropitant concentrations reached steady state approximately after 4 and 8 days following 2 and 8 mg/kg, respectively. The observed drug accumulation ratios were 2.46 and 4.81, after oral administration of 2 and 8 mg/kg, respectively. The exposure of 10 week old puppies to maropitant was lower than that observed in adult dogs, particularly after repeat doses of 1 or 2 mg/kg. 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.

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. In *in vitro* enzyme kinetics data suggest that the non-linear kinetics may be partially associated with saturation of the low capacity enzyme (CYP2D15). Plasma protein binding of maropitant was high (99.5%).

#### Pharmacokinetics (CERENIA Injectable):

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

### DOGS:

The pharmacokinetic (PK) characterization associated with maropitant after a single oral (PO), intravenous (IV), or subcutaneous (SC) dose administration in adult Beagle dogs is provided in the table below.

### Pharmacokinetic Parameters in Beagle Dogs (Mean±SD or Mean and Range)

| PK Parameter                   | SC at 1 mg/kg (n=8)            | IV at 1 mg/kg (n=8)            | PO at 2 mg/kg (n=8) | PO at 8 mg/kg (n=8) |
|--------------------------------|--------------------------------|--------------------------------|---------------------|---------------------|
| AUC <sub>0-24</sub> (hr*ng/mL) | 759.08±189.49                  | 693.83±137.25                  | 561±322             | 7840±5600           |
| C <sub>max</sub> (ng/mL)       | 102.99±46.06                   | 296.62±60.77                   | 81±32               | 776±604             |
| T <sub>1/2</sub> (hr)          | 8.84 <sup>a</sup> (6.15-20.48) | 6.85 <sup>a</sup> (4.87-11.30) | 4.03 (2.48-7.09)    | 5.46 (3.39-7.65)    |
| T <sub>max</sub> (hr)          | 0.56±0.40                      | n/a                            | 1.9±0.5             | 1.7±0.7             |

<sup>a</sup> Harmonic mean

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 1499.13 mL/hr/kg at a dose of 1 mg/kg. 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 characterization associated with maropitant after a single subcutaneous (SC) or intravenous (IV) dose administration in cats is provided in the table below.

### Pharmacokinetic Parameters for a Single Dose in 6-7 Month Old Cats (Mean±SD or Mean and Range)

| PK Parameter                   | SC at 1 mg/kg (n=6)           | IV at 1 mg/kg (n=6)           |
|--------------------------------|-------------------------------|-------------------------------|
| AUC <sub>0-24</sub> (hr*ng/mL) | 2016.07±516.65                | 2116.53±706.72                |
| C <sub>max</sub> (ng/mL)       | 257.84±49.95                  | 987.65±421.75                 |
| T <sub>1/2</sub> (hr)          | 6.57 <sup>a</sup> (5.09-8.60) | 4.86 <sup>a</sup> (3.44-6.79) |
| T <sub>max</sub> (hr)          | 0.43±0.33                     | n/a                           |

<sup>a</sup> Harmonic mean

There appears to be an age-related effect on the pharmacokinetics of maropitant in cats: kittens (4 months) have a higher clearance than adults. In multiple IV and SC studies, the mean maropitant half-life in kittens (4-7 months old) is 7.83 hours, compared to 17.2 hours in 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 (V<sub>ss</sub>) determined after IV administration of 1.0 mg/kg to 6 cats was 510 (388 to 603) mL/hr/kg and 2.3 (1.4 to 3.6) L/kg, respectively. Maropitant displays linear kinetics when administered SC within the 0.25-3 mg/kg dose range. Following SC 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 felino isoenzymes 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 SC 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:

#### Prevention of Acute Vomiting (CERENIA Tablets)

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 stimulus), 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 stimulus) 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 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 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        |
| Day 1 | Placebo (45) | PO            | 22     | 3          | 14%       |
|       |              | SC            | 23     | 16         | 70%       |
|       |              | PO            | 67     | 2          | 3%        |
|       |              | SC            | 41     | 16         | 39%       |
| Day 2 | Placebo (16) | PO            | 7      | 2          | 29%       |
|       |              | SC            | 9      | 6          | 67%       |
|       |              | PO            | 24     | 0          | 0%        |
|       |              | SC            | 13     | 8          | 62%       |
| Day 3 | Placebo (6)  | PO            | 2      | 0          | 0%        |
|       |              | SC            | 4      | 1          | 25%       |
|       |              | PO            | 14     | 0          | 0%        |
|       |              | SC            | 7      | 5          | 71%       |
| Day 4 | Placebo (2)  | PO            | 1      | 0          | 0%        |
|       |              | SC            | 1      | 1          | 100%      |
|       |              | 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 Tablets and Injectable Solution were well tolerated in dogs presenting with various conditions including parvovirus, gastroenteritis, and renal disease. There were no notable differences in mean laboratory values between CERENIA-treated and placebo-treated patients.

CERENIA Tablets were 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 (CERENIA Tablets)

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.

### CERENIA INJECTABLE:

#### DOGS:

In laboratory model studies, CERENIA Injectable Solution administered subcutaneously 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 stimulus), 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 stimulus) 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 canine 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 Injectable Solution, 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 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.

In a laboratory study, thirty-one dogs were subcutaneously administered CERENIA Injectable Solution or saline, at 1 mL/10 kg body weight, 45 minutes prior to administration of an opioid analgesic. Following administration of the opioid analgesic, none of the CERENIA Injectable Solution treated dogs vomited and 93.8% (15/16) of placebo-treated dogs vomited.

The effectiveness of CERENIA administered at 1 mg/kg IV was demonstrated by bridging the results of a PK study to clinical data supporting effectiveness of 1 mg/kg administered SC. The IV and SC administration of a single dose of 1 mg/kg maropitant are equivalent, based on the bioequivalence of the IV and SC AUC<sub>0-12</sub> and justification for the therapeutic equivalence of the IV and SC C<sub>max</sub>.

**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 Injectable Solution 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         | 20.0      |
|           | 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       |

The effectiveness of CERENIA administered at 1 mg/kg IV was demonstrated by bridging the results of a PK study to clinical data supporting effectiveness of 1 mg/kg administered SC. The IV and SC administration of a single dose of 1 mg/kg maropitant are equivalent, based on the bioequivalence of the IV and SC AUC<sub>0-12</sub> and justification for the therapeutic equivalence of the IV and SC C<sub>max</sub>.

**ANIMAL SAFETY:** Laboratory and field studies have demonstrated that CERENIA Tablets are well tolerated in dogs after oral administration.

**Target Animal Safety Study for Acute Vomiting (CERENIA Tablets)**

Fifty six Beagle dogs (28 males and 28 females) approximately 16 weeks of age were administered CERENIA Tablets orally once daily for 15 days at 0, 2, 6, and 10 mg/kg. There were 8 dogs (4 males and 4 females) in the 2 mg/kg group and 16 dogs (8 males and 8 females) in all other groups. CERENIA Tablets caused decreases in food consumption and body weight that were not dose-dependent and did not persist after cessation of treatment.

Beagle dogs approximately 8 weeks of age were administered CERENIA Tablets orally once daily for 15 days at 0, 2, 6, and 10 mg/kg using a protocol similar to the previous study. A dose dependent increase in severity of bone marrow hypoplasia 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, many of the dogs in the study tested positive for coccidia and some tested positive for canine parvovirus.

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 acclimation 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.

Twenty four Beagle dogs (12 males and 12 females) 7 months of age were administered maropitant at doses of 0, 1, 5, and 20 mg/kg orally once daily for 93 consecutive days. Maropitant produced sporadic clinical signs (salivation, emesis), body weight loss, and lower serum albumin levels at 20 mg/kg/day.

Maropitant increased P-R interval, P wave duration, and QRS amplitude in the 20 mg/kg/day dose group. One female in the 20 mg/kg/day group had increased cellularity of the bone marrow. This female was noted to have lower mean red cell parameters (red blood cell count, hemoglobin, hematocrit) and higher platelet counts and reticulocytes.

**Target Animal Safety Study for Motion Sickness (CERENIA Tablets)**

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 parvovirus disease was not definitively diagnosed.

**Tolerance Studies (CERENIA Tablets)**

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.

Twenty-four Beagle dogs (12 males and 12 females) approximately 28 weeks of age were administered maropitant (mesylate salt) orally once daily for 90 days at 0, 1, 5, and 20 mg/kg. End of study body weights in the 20 mg/kg group were 8-15% lower than baseline body weights.

**DOGS (CERENIA INJECTABLE):**

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 Tablets 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 acclimation 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.

Twenty four Beagle dogs approximately 16 weeks of age were administered CERENIA Injectable Solution intravenously once daily for 5 days at 0, 1, and 3 mg/kg (4 females and 4 males per group). CERENIA Injectable Solution was administered at room temperature over 1-2 minutes. Reaction to injection was not specifically recorded. One male dog in the 1 mg/kg group had low hematocrit and white blood cell count on study day 5. One female dog in the 3 mg/kg group had an increased fibrinogen on study day 5. There were no other clinically relevant findings during the study, at necropsy or in histopathology.

**CATS (CERENIA INJECTABLE):**

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 Injectable Solution 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.

Twenty-four healthy domestic short hair cats (12 males and 12 females) approximately 16 weeks of age were administered maropitant at 1 or 3 mg/kg, or saline at 0.1 mL/kg intravenously once daily for 5 days. CERENIA Injectable Solution was administered at room temperature over 1-2 minutes. Reaction to injection was not specifically recorded, but one cat experienced discomfort with accidental extravascular administration. There were no clinically relevant findings during the study, at necropsy or in histopathology.

**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. Each tablet size is packaged in a bottle containing 60 tablets and 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.

Approved by FDA under NADA # 141-262  
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Distributed by:  
 Zoetis Inc.  
 Kalamazoo MI 49007

Based on Cerenia Tablets PI  
 8834091, Revised May 2019; and  
 Cerenia Injectable Solution PI  
 4019387, Revised March 2019

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## In-clinic challenge

Try this in your clinic: Choose a series of canine anesthesia patients and give half of them Cerenia® preoperatively. With the other patients, maintain your regular operative routine.

Then, ask your clinic staff if they can identify which recovering dogs had received Cerenia. Have them look for signs such as return to feeding, panting, and vocalization. Members of the advisory board found that most of the time, clinic staff can identify the happier patients with ease.

***“When I talk to veterinarians and they’re not completely convinced about adding Cerenia on, I say, why don’t you get 5 dogs and give those Cerenia, 5 others don’t. Don’t tell your techs what animal is getting what and just see if they can tell a difference. And pretty much invariably they can. They see that the animal seems to feel more comfortable, they’re eating sooner, and just their demeanor—they can tell the difference.” Dr. David Twedt***

**Try Cerenia in your clinic today to see these results for your patients, your clients, and your team.**

**IMPORTANT SAFETY INFORMATION:** Use Cerenia Injectable subcutaneously for acute vomiting in dogs 2 to 4 months of age or either subcutaneously or intravenously in dogs 4 months of age and older. Safe use has not been evaluated in dogs with gastrointestinal obstruction, or those that have ingested toxins. Use with caution in dogs with hepatic dysfunction. Pain and vocalization upon injection is a common side effect. In people, topical exposure may elicit localized allergic skin reactions, and repeated or prolonged exposure may lead to skin sensitization. See full Prescribing Information, attached.

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(maropitant citrate)

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