Product Name: CERENIA 24MG TABLETS FOR DOGS

APVMA Approval No: 62423/113149

RLP APPROVED

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Label Name:	CERENIA 24MG TABLETS FOR DOGS

Signal Headings:	PRESCRIPTION ANIMAL REMEDY KEEP OUT OF REACH OF CHILDREN FOR ANIMAL TREATMENT ONLY

Constituent Statements:	24 mg/Tb MAROPITANT AS MAROPITANT CITRATE

Claims:	For the prevention of nausea and acute vomiting in dogs and puppies 8 weeks of age or older and the prevention of vomiting due to motion sickness in dogs 16 weeks of age or older.

Net Contents:	4 Tablets

Directions for Use:	

Restraints:	NOT TO BE USED in food producing species of animals.

Contraindications:	The safety of CERENIA has not been established during pregnancy and lactation and in puppies less than 8 weeks of age and thus CERENIA is not recommended for these classes of dog. It is recommended that a benefit/risk assessment be carried out and discussed with the owner.

Precautions:	Emesis can be associated with serious, severely debilitating conditions such as gastrointestinal obstruction, and the cause should be investigated. Products such as CERENIA should be used in conjunction with other supportive measures such as fasting, dietary control and fluid therapy while the aetiology is being determined. CERENIA should not be used concomitantly with Ca-channel antagonists as maropitant has affinity for Ca-channels. Maropitant is metabolised in the liver and therefore should be used with caution in dogs with liver disease.

	Maropitant is highly bound to plasma proteins and may compete with other highly bound drugs. The risk of adverse events should be considered in cases of hypoproteinaemia, reduced protein binding ability (eg aged dogs) or when other highly bound drugs are being used. CERENIA should be used with caution in animals suffering from or with a predisposition to heart diseases. Margin of safety studies indicate that use of CERENIA at above-label dose rates in 8 to 16 week old puppies may be associated with loss of bodyweight and bone marrow hypocellularity. These effects may be more pronounced in younger puppies. The veterinarian should assess the benefits of emesis control in young puppies noting that the effect of CERENIA use on survival outcomes of dogs with gastrointestinal infections (e.g. Canine Parvovirus, coccidia) has not been studied.

Side Effects:	Symptoms of overdosage at 20mg/kg include vomiting on administration, salivation and watery faeces.

Dosage and Administration:	In use shelf life: Half tablets should be stored for a maximum of two days after removal from the blister. Half tablets should be returned to the opened blister and kept within the cardboard outer. General Instructions: Vomiting can be a side effect of CERENIA treatment and a light meal or snack approximately one hour before dosing will reduce the incidence. A higher incidence of vomiting is noted from dosing on an empty stomach and thus prolonged fasting before administration should be avoided. If vomiting does occur prior to travel, repeat dosing should be withheld. CERENIA Tablets should not be administered wrapped or encapsulated in food as this may delay dissolution of the tablet and consequently the onset of the effect. Dogs should be carefully observed following administration to ensure that each tablet is swallowed. CERENIA is non-sedating and should not be used where sedation is required. The assessment of the severity of nausea is subjective, and the efficacy of the product is likely to be more variable against nausea than emesis. As such, this product should be used under close veterinary supervision and subsequent to a comprehensive clinical examination. Product use may need to be in conjunction with other supportive measures such as dietary management and most importantly treatment of the underlying cause. For Prevention of Nausea and Acute Vomiting: Administer CERENIA Tablets orally at a minimum dose of 2 mg per kg bodyweight once daily for up to fourteen consecutive days. To prevent nausea and vomiting, CERENIA Tablets should be administered more than one hour in advance. The duration of effect is approximately 24 hours and therefore treatment can be given the night before administration of an agent that may cause nausea or emesis e.g. chemotherapy. (Insert Table 1) CERENIA Tablets may be used interchangeably with CERENIA Injectable Solution for once daily dosing for the prevention of acute vomiting. For Prevention of Vomiting due to Motion Sickness in dogs 16 weeks of age and older: Administer CERENIA Tablets orally at a dose of 8 mg per kg bodyweight once daily for up to two consecutive days. Administer CERENIA Tablets at least one hour prior to travel. Do not redose if vomiting is observed. The duration of effect is at least 12 hours, which may allow administration the night before early morning travel. (Insert table 2) Studies have shown an efficacy of 93% in preventing motion sickness.

General Directions:	Pharmacology Pharmacokinetics The pharmacokinetic profile of maropitant when administered as a single oral dose of 2 mg/kg body weight to dogs was characterised by a maximum concentration (Cmax) in plasma of approximately 81 ng/ml; this was achieved within 1.9 hours post-dosing (Tmax). Peak concentrations were followed by a decline in systemic exposure with an apparent elimination half-life (t0.5) of 4.03 hours. At a dose of 8 mg/kg, Cmax of 776 ng/ml was reached at 1.7 hours post-dosing. The elimination half-life at 8 mg/kg was 5.47 hours. The inter-individual variation in kinetics may be large, up to 70 CV% for AUC. During clinical studies maropitant plasma levels conferred efficacy from 1 hour after administration. Estimates for the oral bioavailability of maropitant were 23.7% at 2 mg/kg and 37.0% at 8 mg/kg. The volume of distribution at steady-state (Vss) determined after intravenous administration at 1–2 mg/kg ranged from approximately 4.4 to 7.0 l/kg. Maropitant displays non-linear pharmacokinetics (AUC increases more than proportionally with increasing dose) when administered orally within the 1–16 mg/kg dose range. Following repeated oral administration for five consecutive days at a daily dose of 2 mg/kg, accumulation was 151%. Following repeated oral administration for two consecutive days at a daily dose of 8 mg/kg, accumulation was 218%. Maropitant undergoes cytochrome P450 (CYP) metabolism in the liver. CYP2D15 and CYP3A12 were identified as the canine isoforms involved in the hepatic biotransformation of maropitant. Renal clearance is a minor route of elimination, with less than 1% of an 8 mg/kg oral dose appearing in the urine as either maropitant or its major metabolite. Plasma protein binding of maropitant in dogs is more than 99%. Pharmacodynamics Vomiting is a complex process coordinated centrally by the emetic centre 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 (NK1) receptor antagonist which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. Substance P is found in significant concentrations in the nuclei comprising the emetic centre and is considered the key neurotransmitter involved in emesis1. By inhibiting the binding of substance P within the emetic centre, 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 anti-emetic effectiveness against both central and peripheral emetogens including apomorphine, cisplatin, and syrup of ipecac. 1Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. [Review] [60 refs]. Drugs. 2000;60:533-46. Effectiveness Prevention of Acute Vomiting In laboratory model studies, CERENIA Tablets administered at 2 mg/kg BW reduced the number of emetic events associated with established neural (central) and humoral (peripheral) stimuli. Following administration of apomorphine (central emetic stimuli), vomiting was observed in 33% (4 of 12) of dogs treated with CERENIA Tablets and 100% (12 of 12) of Beagle dogs treated with placebo tablets. Following administration of syrup of ipecac (peripheral emetic stimuli) vomiting was observed in 33% (4 of 12) of 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. 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. Prevention of Vomiting due to Motion Sickness In a study of canine veterinary patients taken on a one-hour car journey and treated with either CERENIA Tablets at a minimum dose of 8 mg/kg BW or placebo tablets 2 hours prior to the journey, 67 of 122 (55%) of dogs vomited during the journey when treated with placebo while 8 of 122 (7%) vomited during the journey after treatment with CERENIA Tablets. The probability that a dog in this study, prone to motion sickness would NOT vomit during a journey if treated with CERENIA Tablets was 93%, while the probability was 48% if treated with placebo. Animal Safety Laboratory and field studies have demonstrated that CERENIA Tablets are well tolerated in dogs after oral administration. Target Animal Safety for Acute Vomiting 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 bodyweight 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 one tested positive for parvovirus. Target Animal Safety for Motion Sickness Forty Beagle dogs (20 males and 20 females) between 16 – 18 weeks of age were administered CERENIA Tablets orally once daily for five 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 haemoconcentration, but the effects on feed consumption, body weight and RBC's 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 complicatedacclimated to the test facility, many of the dogs in the study tested positive for coccidia. Additionally, some dogs in the study tested positive for canine parvovirus, however, clinical parvoviral disease was not definitively diagnosed. In clinical field studies in veterinary patients, CERENIA Tablets 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. In clinical trials, 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 but specific drug interactions with these and other concurrent medications were not investigated.

First Aid Instructions:	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

First Aid Warnings:	

Disposal:	Dispose of empty container by wrapping with paper and putting in garbage.

Storage:	Store below 30°C (Room Temperature).

Dosage and Administration Tables

Table 1

Dog body weight (kg)	Number of tablets			(Dose range supplied mg/kg)
	16 mg	24 mg	60 mg	
3.0 – 4.0 *	½			2-2.7
4.1 – 8.0	1			2-3.9
8.1 – 12.0		1		2-3.0
12.1 – 24.0		2		2-4.0
24.1 – 30.0			1	2-2.5
30.1 – 60.0			2	2-4.0

* Correct dose for dogs of less than 3 kg cannot be accurately achieved with tablets

Table 2

Dog body weight (kg)	Number of tablets				(Dose range supplied mg/kg)
	16 mg	24 mg	60 mg	160 mg	
0.8 – 1.0	½				8-10.0
1.1 – 1.5		½			8-10.9
1.6 – 2.0	1				8-10.0
2.1 – 3.0		1			8-11.4
3.1 – 4.0	2				8-10.3
4.1 – 5.0	2½				8-9.8
5.1 – 6.0		2			8-9.4
6.1 – 7.5			1		8-9.8
7.6 – 10.0				½	8-10.5
10.1 – 11.3			1½		8-8.9
11.4 – 15.0			2		8-10.5
15.1 – 20.0				1	8-10.6
20.1 – 22.5			3		8-9.0
22.6 – 30.0				1½	8-10.6
30.1 – 40.0				2	8-10.6
40.1 – 50.0				2½	8-10.0
50.1 – 60.0				3	8-9.6