618409

Pr Emavert®

DIN 02529564

Maropitant injection
Veterinary Use Only

Sterile

Antiemetic for cats and dogs

DESCRIPTION: Maropitant is a potent and selective neurokinin (NK1) receptor antagonist that blocks the pharmacological action of substance P in the CNS. Maropitant is the non-proprietary designation for a substituted quinuclidine. The chemical name is (2S,3S,9S-(5-(1,1-dimethylethyl)-2-methoxyphenylmethyl)-2-phenylpiperidine, (2-phenyl-3-(2-methoxy-5-tert-butylbenzyl)-1-azabicyclo[2.2.2]octane-3-endo-hydroxy-1,2,3- propanetricarboxylate monohydrate.
The chemical structure of maropitant is:

Each mL of Emavert contains 10 mg of maropitant base as the medicinal ingredient, 11.1 mg benzyl alcohol as a preservative, citric acid, betadex sulfobutyl ether sodium (also called sulfobutylether-β-cyclodextrin or SBECD), sodium hydroxide for pH adjustment and water for injection.

INDICATIONS:
Dogs: For the symptomatic treatment of acute vomiting (e.g. parvovirus infection, gastro-enteritis and pancreatitis) and the prevention of vomiting associated with the use of an emetogenic medication (e.g. chemotherapy, anesthesia).
Cats: For the symptomatic treatment of acute vomiting.

DOSAGE AND ADMINISTRATION:
Dogs: For the symptomatic treatment of acute vomiting in dogs:
Dogs 15 weeks to 4 months of age: administer Emavert intravenously over 1-2 minutes or subcutaneously at 1 mg/kg equal to 1 mL/10 kg bodyweight once daily for up to 5 days.
Dogs 4 months of age and older: administer Emavert intravenously over 1-2 minutes or subcutaneously at 1 mg/kg equal to 1 mL/10 kg body weight once daily for up to 5 days.
Emavert may be used interchangeably with maropitant citrate tablets for once daily dosing of the acutely vomiting dogs. The dose (and duration of treatment) is different depending on the formulation.
For the prevention of vomiting associated with the use of an emetogenic medication in dogs 4 months of age and older: administer Emavert intravenously over 1-2 minutes or subcutaneously at 1 mg/kg equal to 1 mL/10 kg body weight one time, 60 minutes prior to a pre-anesthetic drug or 60 minutes prior to chemotherapy.
Cats: For the symptomatic treatment of acute vomiting in cats 4 months of age and older: administer Emavert intravenously over 1-2 minutes or subcutaneously at 1 mg/kg equal to 1 mL/10 kg body weight once daily for up to 5 days.
Store unused preparation at room temperature (15-30°C) or refrigerated temperature (2-8°C).

CONTRAINDICATIONS: Emavert is contraindicated in dogs and cats suspected of having a gastrointestinal obstruction or toxin ingestion. Immediate treatment with Emavert is not recommended in cats with severe renal impairment.

CAUTION: Safety in dogs and cats used for breeding, pregnant, or lactating bitches and queens has not been established. The safety in dogs or kittens less than 16 weeks of age has not been established (See ANIMAL SAFETY section for complete information).
Clinical trials demonstrated that Emavert is well tolerated in healthy young adult dogs and cats. Therefore, extensive safety evaluations should be employed. Hypovolemia in combination with maropitant may increase the risk for hypotension; all dogs and cats with ongoing emesis should receive rehydration therapy.
Emavert should be used with caution in dogs and cats with bradycardia or underlying heart disease since maropitant may increase the risk of arrhythmias.
A mild and transient hypotension can occur shortly after IV administration in dogs.
Maropitant is metabolized in the liver and therefore should be used with caution in dogs and cats with hepatic disease.
Vomiting may mask the onset of adverse effects of other drugs administered concurrently; other drugs that are highly protein bound. Drug interactions between maropitant injectable and other drugs have not been adequately investigated in dogs and cats.
Hypoproteinemic dogs and cats being treated with maropitant should be monitored closely; if adverse effects are seen, treatment should be discontinued.
If maropitant therapy has not been effective after 5 days of use, alternative treatment to control nausea should be pursued.
The concurrent use of maropitant with other antiemetic agents has not been assessed in dogs and cats.
Food consumption and weight gain of puppies being treated with Emavert should be closely monitored. Anorexia and weight loss may occur. Emavert causes dose related decreases in appetite and body weight. In puppies younger than 11 weeks of age, histological evidence of bone marrow hypocellularity was observed in dogs given maropitant at 3 times the recommended dose. Bone marrow hypocellularity was not observed in puppies, 15 weeks and older, bone marrow hypocellularity was not observed (see ANIMAL SAFETY section).

WARNINGS: In case of accidental injection or exposure, seek medical advice. Topical exposure may elicit localized allergic skin reactions in some individuals.
Accidental injection into the paw of a human may cause temporary pain, swelling and redness which may last for several days if not treated with an opioid analgesic.
In case of accidental eye exposure, flush with water for 15 minutes and seek medical attention. Keep out of reach of children.

ADVERSE REACTIONS Pain at injection site may occur when injected subcutaneously. In cats, moderate to severe response to injection has been frequently reported from the use of maropitant citrate injectable solution.
In very rare cases, anaphylactic type reactions (allergic oedema, urticaria, erythema, collapse, dyspnea, pale mucosa membranes) may occur. Lethargy, anorexia and diarrhea have been observed shortly after the use of the product and generally resolve within 24 hours without treatment or after the underlying cause for the vomiting is corrected.
Post Market Experience: The following adverse events are based on post-approval adverse drug experience reporting with maropitant citrate injection. Not all adverse events reported have a clear causal relationship to drug exposure. Adverse events are listed in descending order of reporting frequency by body system(s) using this data. The following adverse events have been reported in decreasing order of reporting frequency (by body system):
• Application site – injection site pain, injection site oedema
• Systemic – lethargy, anorexia
• Immune – allergic oedema, urticaria, anaphylaxis
• Cardiovascular – collapse, pale mucous membranes
• Respiratory tract – vomiting, hypersalivation, diarrhea
• Skin and appendages – erythema, pruritus
• Behavioural – vocalization, hyperactivity

CLINICAL PHARMACOLOGY:
Pharmacokinetics Emavert formulated using sulfobutylether-β-cyclodextrin (SBECD), which exhibits enhanced binding to maropitant at refrigerated temperatures. The enhanced binding affinity reverses rapidly upon warming. Therefore, although the initial rate of systemic drug absorption may vary as a function of injected formulation temperature, the ultimate systemic drug exposure is not affected by the formulation temperature when administered as an intravenous bolus.
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)
$AUC_{0-\infty}$ (hr*ng/mL)	759.08±189.49	693.83±137.25	501±322	7840±5600
C_{max} (ng/mL)	122.99±46.06	296.62±60.77	81±32	776±604
$T_{1/2}$ (hr)	8.64* (6.15-20.48)	6.85* (4.87-11.30)	4.03 (2.48-7.09)	5.46 (3.39-7.65)
T_{max} (hr)	0.56±0.40	n/a	1.9±0.5	1.7±0.7

*Harmonic mean

The 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 increased with the dose, the plausible cause of this increase was the saturation of the liver and the reticulum. Dogs 1 year and older 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 when the dose is increased from 2 to 8 mg/kg PO. Systemic clearance of maropitant following IV administration was 149L/10 kg/hr and 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 (PO) mg/kg. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve ($AUC_{0-\infty}$) increased with the administered dose. A dog CYP isozyme, 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 (20-80 mg/kg PO), dose proportionality is re-established. Based upon in vitro binding data, maropitant is highly bound to dog plasma proteins (99.5%). Maropitant is highly bound to dog tissues (distribution volume at steady state is 22L/kg or about 16 times the dog BW). Based on differences in plasma trough concentrations from a single study, the exposure in old puppies to maropitant may be lower than that observed in adult dogs, particularly after doses of 1 or 2 mg/kg.
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=8)	IV at 1 mg/kg (n=8)
$AUC_{0-\infty}$ (hr*ng/mL)	2016.07±516.65	2116.53±706.72
C_{max} (ng/mL)	257.84±49.95	987.65±421.75
$T_{1/2}$ (hr)	6.33* (5.09-8.60)	4.66* (3.44-6.78)
T_{max} (hr)	0.56±0.40	n/a

*Harmonic mean

Maropitant clearance is an age-related effect on the pharmacokinetics of maropitant in cats. Kittens have a higher clearance than adults. In multiple IV and SC studies, the mean maropitant clearance in young healthy cats ranged from 20 to 40 L/hr/kg, depending on age, while in adult cats it was consistently lower. Systemic clearance after intravenous administration in cats was 91.3%. The mean total body clearance (Cl) and volume of distribution at steady-state (Vss), determined after intravenous administration of 1 mg/kg maropitant to young healthy cats, was 0.25 L/hr/kg and 1.6 L/kg, respectively. The mean terminal half-life ($T_{1/2}$) was approximately 6 hours. Maropitant was quickly absorbed after SC administration of once daily doses of 1 mg/kg body weight for 5 consecutive days, no accumulation of maropitant occurred. Maropitant underwent cytochrome P450 (CYP) metabolism in the liver. CYP1A and CYP3A-related enzymes were identified as the feline isoforms involved in the hepatic metabolism of maropitant. The major metabolite was a carboxylic acid derivative. Based on in vitro studies 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 parent compound, 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%.
Pharmacodynamics Emesis is a complex process coordinated centrally by the emetic centre located in the medulla oblongata, which receives afferent inputs from various nerve pathways, including those originating in the gastrointestinal tract, the vestibular system, and the cerebral cortex. Stimulation of the emetic centre results in the activation of efferent pathways to the abdominal muscles, diaphragm, and the stomach, which ultimately results in the expulsion of the stomach contents. Maropitant is a competitive receptor antagonist at the human NK1 receptor and considered the key neurotransmitter involved in emesis. Maropitant is a neurokinin 1 (NK1) receptor antagonist which acts by inhibiting the binding of substance P within the emetic center. A variety of in vitro assays have demonstrated that maropitant displays potent and selective binding at the NK1 receptor with a corresponding lack of significant activity at other receptors.
ANIMAL SAFETY: Laboratory studies and clinical field evaluations have demonstrated that maropitant is well tolerated in young adult dogs and cats after subcutaneous and intravenous administration.
Dogs: In a laboratory study, maropitant citrate injection was administered subcutaneously to 56 healthy 16-week-old Beagle dogs for 15 days at 0, 1, 3 and 9 mg/kg. There were 8 puppies in each treated and 4 puppies in the 1 mg/kg group and 16 puppies (8 males and 8 females) in all other groups. The primary treatment-related findings were a dose-dependent increase in frequency and severity of bone marrow hypoplasia was observed histologically and correlated with weight loss in the 3 and 9 mg/kg groups with 3 of 16 dogs treated with 9 mg/kg/day. Additionally, the activated partial thromboplastin time (aPTT) was prolonged (67 to 3 seconds, reference range 15-25 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. Bone marrow hypocellularity was not observed in 6 week old puppies administered maropitant at 3 times the recommended dose for 15 days, but was observed in 15 week old puppies treated with the same dose and for the same duration as in the previous study. The primary treatment-related findings were pain upon administration and dose dependent minimal to moderate injection site irritation and swelling. A dose dependent increase in frequency and severity of bone marrow hypoplasia was observed histologically and correlated with weight loss in young adult dogs given 3 times the recommended dose for 15 consecutive days. Bone marrow hypocellularity was not observed in 6 week old puppies but was diagnosed with suppurative pancreatitis and esophagitis. Interpretation of the study results is complicated by the health status of study animals. Dogs used in the study were weaned early, minimally acclimated to the test facility, and many of the dogs in the study tested positive for coccidia.
In a laboratory study, maropitant citrate injection was administered subcutaneously to 56 healthy 15-week-old Beagle dogs for 15 days at 0 mg/kg for 2 days, placebo (saline) subcutaneously (SC) for 5 days, maropitant citrate injection at 1 mg/kg SC for 5 days, or maropitant citrate 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 citrate injections compared to saline. Mates and cohoused dogs showed more pain than single housed dogs. Injection site swelling was observed in 1 of 8 dogs treated with 1 mg/kg maropitant citrate injection. No treatment related changes were observed in the hematology, clinical chemistry, or urinalysis parameters. Bone marrow hypocellularity was observed in 4 of 8 dogs treated dogs (50 %) versus 0 of 8 dogs in the saline treated group. Mild hypocellular femoral bone marrow was seen in 1 male that received 1 mg/kg maropitant SC for 5 days, reticulocyte counts were not available for this dog. The food consumption and body weights were variable in many puppies throughout the study.
Maropitant citrate injection was administered intravenously to 24 Beagle dogs approximately 16 weeks of age once daily for 5 days at 0, 1, and 3 mg/kg (4 females and 4 males in each group). Maropitant citrate was administered over 1 minute. Injection site reactions were observed in 2 of 8 dogs given 3 mg/kg (1 female and 1 male dog in the 1 mg/kg group had two hematoma 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, all necropsy or histopathology.

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In a U.S. 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 maropitant citrate injection at 1.1 mg/kg subcutaneous (n=4) or intravenous (n=73).

Frequency of adverse reaction by treatment				
Adverse reaction	Placebo (n=41)		Maropitant citrate injection (n=77)	
	# dogs	% occurrence	# dogs	% occurrence
Diarrhea	3	7.3	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 U.S. field study for the prevention and treatment of acute vomiting in dogs treated with 1.0 mg/kg maropitant citrate injection subcutaneously and/or maropitant citrate tablets at 2 mg/kg once daily for up to 5 consecutive days:

Adverse reaction	Placebo (n=68)		Maropitant citrate injection (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
Crisis/Chorioiditis	0	0	3	1.5
Endotoxic shock	1	1.4	1	0.5
Hematuria	0	0	2	1
Excoriation	0	0	2	1
Lack of efficacy	3	8.7	5	2.4

Other clinical signs were reported but were <3.5% of dogs.
During clinical studies, maropitant citrate was safely used in dogs in combination with other veterinary products (e.g., fluid and electrolyte replacement solutions, parenteral antibiotics, gastro-protectants, and pain relievers).
Cats: In a laboratory study, maropitant citrate injection was administered subcutaneously for 5 consecutive days to maropitant 16 weeks of age once daily for 15 days at 0, 1, 3, and 9 mg/kg. There were 8 cats (4 males and 4 females) in each dose group. Treatment-related, dose-dependent findings were: pain upon administration, injection site reactions (swelling and/or pain), and increased incidence of bone marrow hypoplasia. Injection site reactions were observed in one or more of the injection sites was observed in 1 of 8 cats treated at 1 mg/kg, 7 of 8 cats treated at 3 mg/kg, and 7 of 8 cats treated at 9 mg/kg. There was a statistically significant reduction (p = 0.0171) in food intake at 9 mg/kg compared to placebo cats. One cat at 9 mg/kg was lethargic on days 12, 13 and 14 of the study. All necropsies were normal. There was no treatment-related gross lesions. Histopathological evaluation of injection sites showed no lesions at a dose-dependent frequency.
In another laboratory study, maropitant citrate injection was administered intravenously to 24 healthy domestic shorthair cats approximately 16 weeks of age once daily for 5 days at 0, 1, and 3 mg/kg (4 females and 4 males in each dose group). Maropitant citrate injection 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 treatment-related effects on food consumption, fecal scores, or clinical pathology parameters.
The following adverse reactions were reported during the course of a U.S. field study for the treatment of vomiting in cats treated with 1.0 mg/kg maropitant citrate injection subcutaneously once daily for up to five consecutive days:

Frequency of adverse reaction by treatment				
Adverse reaction	Placebo (n=62)		Maropitant citrate injection (n=133)	
	# cats	% occurrence	# cats	% occurrence
Moderate response to injection[1,2]	1	1.6	30	22.6
Significant response to injection[1,3]	1	1.6	15	11.3
Fever/Pyrexia	2	3.2	2	1.5
Dehydration	0	0	3	2.3
Diarrhea	0	0	2	1.5
Diarrhea	4	6.5	2	1.5
Conjunctivitis	0	0	2	1.5

[1] The clinician observed and graded each cat's response to injection.
[2] Cat objected to the injection by retreating and scuffing.
[3] Cat objected to the injection by retreating, hissing, scratching, and vocalization.
The adverse events with occurrence of <1% included: injection site pain, anorexia, hematochezia, hematuria and hypersalivation.

EFFICACY:
In a laboratory emetic model studies, maropitant citrate injection significantly reduced the number of emetic events associated with established neural (central) and peripheral (visceral) stimuli.
In vivo studies in dogs demonstrated the antiemetic efficacy of maropitant against central and peripheral emetics including apomorphine, cisplatin and syrup of ipecac. Maropitant also significantly reduced the number of emetic episodes induced by the cancer chemotherapy agents cisplatin, cyclophosphamide, doxorubicin, and vincristine.
In a laboratory study, maropitant citrate injection administered subcutaneously for 5 days at 1 mg/kg SC reduced emesis by 93.3% (30 of 32 dogs treated with cisplatin) versus 6.25% (2 of 32) of placebo-treated dogs.
In a U.S. study, canine patients were treated with maropitant citrate injection or placebo administered either 1 hour prior to cisplatin (cisplatin administered in 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 maropitant citrate injection vs. 17.1% (6/35) of the dogs administered placebo did not vomit during the 5 hour post-treatment observation period. Similarly, 71% (28/39) of the dogs administered maropitant citrate injection and 5.71% (2/35) of the dogs administered placebo did not vomit during the 5 hour post-treatment observation period. Further evidence of vomiting following treatment was not observed.
In a U.S. field study was conducted using 275 canine patients presented to veterinary hospitals with a history of acute vomiting associated with various conditions (including parvovirus enteritis, gastroenteritis, food indiscretion, pancreatitis, renal disease or hepatitis). The vomiting was observed on Day 0. In this study, both maropitant citrate injection and tablets were well tolerated and there were no notable differences in mean laboratory values between maropitant-treated and placebo-treated dogs.
Percent of Vomiting For Each Study Day, Based Upon Treatment and Route of Administration

Days	Treatment	Route	# dogs	# vomited	% vomited
Day 0	Placebo (63)	SC	63	19	30%
	Maropitant (182)	SC	182	18	10%
Day 1	Placebo (64)	PO	26	4	15%
		SC	27	17	63%
	Maropitant (182)	PO	96	3	3%
		SC	46	17	37%
Day 2	Placebo (63)	PO	13	2	15%
		SC	9	6	67%
	Maropitant (170)	PO	40	0	0%
		SC	14	9	64%
Day 3	Placebo (55)	PO	2	0	0%
		SC	5	1	20%
	Maropitant (165)	PO	16	0	0%
		SC	6	4	67%
Day 4	Placebo (18)	PO	1	0	0%
		SC	1	1	100%
	Maropitant (73)	PO	7	1	15%
		SC	2	1	50%

In a laboratory study, 31 dogs were subcutaneously administered maropitant citrate injection or saline, at 1 mg/kg body weight, 45 minutes prior to administration of an opioid analgesic (morphine as pre-anesthetic to routine surgery (castration/spay). Following administration of the opioid analgesic, none of the maropitant citrate injection-treated dogs vomited and 93.8% (15/16) of placebo-treated dogs vomited during the pre-operative period.
The efficacy of maropitant citrate injection administered by intravenous (IV) was demonstrated by bridging the results of a U.S. clinical study supporting effectiveness at 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 dosages. The IV and SC administration of 1 mg/kg are bioequivalent.
Cats: In a laboratory model study, maropitant citrate injection administered to cats at a dosage of 1.0 mg/kg, prevented vomiting for a full 24-hour period. Following administration of the emetogen ipecac 210 hours after antiemetic treatment, 33% (4 of 12) of maropitant citrate injection-treated cats vomited once each while 100% (12 of 12) of placebo-treated cats vomited 2 to 6 times each.
In a U.S. field study was conducted using 195 feline patients presented to veterinary hospitals with a history of acute vomiting. These were diagnosed with gastroenteritis, pancreatitis, inflammatory bowel disease, neoplastic disease and hepatic lipidosis. They were treated with maropitant citrate injection or placebo (n = 62) administered subcutaneously (SC) for 5 days, at 1 mg/kg. The vomiting was observed on Day 0. In this study, both treatments were given 24 hours for up to five consecutive days, at the discretion of the clinician. 133 cats were treated with maropitant citrate injection-treated cats (1.6%) vomited one time each and 12 placebo-treated cats (20.3%) vomited a combined total of 20 times in the first 24 hours post treatment.
Percent of Cats Vomiting For Each Study Day by Treatment

Study Day	Treatment	# cats	# vomited	% vomited
0	Placebo	59	12	20.3
	Maropitant	123	2	1.6
1	Placebo	21	5	23.8
	Maropitant	35	1	2.9
2	Placebo	9	2	22.2
	Maropitant	10	0	0
3	Placebo	5	0	0.0
	Maropitant	6	0	0.0
4	Placebo	3	0	0.0
	Maropitant	2	0	0.0

The efficacy of maropitant citrate injection administered at 1 mg/kg IV was demonstrated by bridging the results of a PK study to clinical data supporting effectiveness at 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 $AUC_{0-\infty}$ and justification for the therapeutic equivalence of the IV and SC C_{max}.
STORAGE: Store between 15 and 25°C. Content should be used within 90 days after first opening of the vial.
PRESENTATION: Emavert is available in 20-mL amber vials.

MANUFACTURED BY: Dechra Veterinary Products, Inc., The Netherlands
IMPORTED AND DISTRIBUTED BY: Dechra Veterinary Products Inc., 1 Holiday Ave, East Tower, Suite 340, Pointe-Claire, Quebec, H9R 5N3, Canada

Dechra

618409

Pr Emavert®

DIN 02529564

Maropitant pour injection
Usage vétérinaire seulement

Stérile

Antiémétique pour chats et chiens

DESCRIPTION Le maropitant est un antagoniste puissant et sélectif des récepteurs de la neurokinine (NK1) 1 bloque l'action pharmacologique de la substance P dans le système nerveux central. Le maropitant est la dénomination non-propriétaire d'une quinuclidine substituée. Le nom chimique est (2S,3S,9-(5-(1,1-dimethylethyl)-2-methoxyphenylmethyl)-2-phenylpiperidine, (2-phenyl-3-(2-methoxy-5-tert-butylbenzyl)-1-azabicyclo[2.2.2]octane-3-endo-hydroxy-1,2,3- propanetricarboxylate monohydrate.
La structure chimique du chlorure de maropitant est illustrée ci-dessous.

Chaque mL d' Emavert contient 10 mg de maropitant comme ingrédient médicinal et 11,1 mg d'alcool benzylique comme agent de conservation, de l'acide citrique, du bétadex sulfobutyl éther sodique (aussi appelé sulfobutylether-β-cyclodextrin ou SBECD), de l'hydroxyde de sodium pour ajuster le pH et de l'eau pour injection.

INDICATIONS : Chiens : Pour le traitement symptomatique des vomissements aigus (p.ex., infection par le parvovirus, gastro-entérite, pancréatite) et la prévention des vomissements associés à l'emploi d'un medicament émétogène (p. ex., chimothérapie, anesthésie).
Chats : Pour le traitement symptomatique des vomissements aigus.

POSOLOGIE ET MODE D'ADMINISTRATION :
Chiens : Pour le traitement symptomatique des vomissements aigus :
Chiens âgés de 15 semaines à 4 mois : administrer Emavert par voie sous-cutanée à la dose de 1 mg/kg (1 ml/10 kg), une fois par jour durant un maximum de 5 jours.
Chiens âgés de 4 mois ou plus : Administrer Emavert par voie intraveineuse sur une durée de 1 à 2 minutes ou par voie sous-cutanée à la dose de 1 mg/kg (1 ml/10 kg), une fois par jour durant un maximum de 5 jours.
La solution injectable Emavert et les comprimés de chlorure de maropitant sont interchangeables. Lors du traitement ponctuel (une série administrée une fois par jour pendant 5 jours) des chiens souffrant de vomissements aigus, le dosage et la durée du traitement varient selon la formulation.
Pour la prévention des vomissements associés à l'emploi d'un medicament émétogène chez les chiens âgés de 4 mois ou plus : Administrer Emavert par voie intraveineuse sur une durée de 1 à 2 minutes ou par voie sous-cutanée à la dose de 1 mg/kg (1 ml/10 kg), une fois, 60 minutes avant l'emploi d'un medicament anesthésique ou 60 minutes avant une chimothérapie.
Chats : Pour le traitement symptomatique des vomissements aigus chez les chats âgés de 4 mois ou plus : Administrer Emavert par voie intraveineuse sur une durée de 1 à 2 minutes ou par voie sous-cutanée à la dose de 1 mg/kg (1 ml/10 kg), une fois par jour durant un maximum de 5 jours.
Emavert peut être administré à température ambiante (15-30°C) ou réfrigérée (2-8°C).

CONTRE-INDICATIONS Emavert est contre-indiqué chez les chiens et les chats chez lesquels une obstruction gastro-intestinale ou l'ingestion d'une toxine sont soupçonnées. Le traitement immédiat avec Emavert n'est pas recommandé chez les chats souffrant d'insuffisance rénale sévère.

PRÉCAUTIONS : L'innocuité du produit chez les chiennes et les chats de reproduction, les chiennes et les chattes gestantes ou allaitantes, les chots âgés de moins de 16 semaines et les chatons âgés de moins de 16 semaines n'a pas été établie. Pour plus d'information, consulter la rubrique INNOCUITÉ POUR L'ANIMAL.
Les vomissements peuvent être associés des différentes maladies sous-jacentes; les éléments diagnostiques appropriés devraient donc être utilisés.
L'administration du maropitant en présence d'hypovolémie peut accroître le risque d'hypotension; tous les chiens et les chats présentant des vomissements devraient recevoir une thérapie de réhydratation.
Emavert doit être administré avec prudence chez les chiens et les chats présentant une bradycardie ou une maladie cardiaque sous-jacente, puisque le maropitant peut accroître le risque d'arythmie.
Une hypotension légère et transitoire peut se produire peu après l'administration intraveineuse chez les chiens.
Le maropitant est métabolisé dans le foie et doit donc être administré avec prudence aux chiens et aux chats présentant une atteinte hépatique.
Les vomissements peuvent masquer le début des effets indésirables des autres médicaments administrés en même temps; les médicaments hautement liés aux protéines. Les interactions médicamentaires entre le maropitant injectable et d'autres médicaments n'ont pas été étudiées de façon approfondie chez les chiens et les chats.
Les chiens hypoprotéinémiques traités au maropitant doivent être surveillés de près; si des effets indésirables apparaissent, le traitement devrait être interrompu si des effets indésirables sont observés.
Si le traitement au maropitant ne semble pas efficace après 3 jours, un autre traitement doit être envisagé.
L'administration concomitante du maropitant et d'autres antiémétiques n'a pas été évaluée chez chiens et les chats.
La consommation alimentaire et le gain pondéral des chiots traités avec Emavert doivent faire l'objet d'une surveillance étroite. L'anorexie et la perte de poids surviennent de façon différente selon la dose administrée aux chiots âgés de moins de 11 semaines. Chez des chiots âgés de moins de 11 semaines, l'hypocellularité de la moelle osseuse plus fréquente et plus grave chez des chiots traités avec maropitant, comparativement aux chiots témoins. L'hypocellularité de la moelle osseuse n'a pas été observée chez les chiots âgés de 15 semaines et plus (soumise à rubrique INNOCUITÉ POUR L'ANIMAL).
EFFETS INDÉSIRABLES En cas d'injection ou d'exposition accidentelle, consulter un médecin. L'application locale peut provoquer des réactions allergiques cutanées locales chez certaines personnes.
Accidentelle injection dans la patte d'un humain peut causer une douleur temporaire, gonflement et rougeur qui peuvent persister plusieurs jours si non traités avec un analgésique opioïde. Garder hors de la portée des enfants.
RÉACTIONS INDÉSIRABLES : De la douleur au site d'injection pourrait survenir lorsqu'injecté sous-cutané. Chez les chats, une réponse modérée à sévère à la suite d'une injection sous-cutanée de la solution injectable de chlorure de maropitant a été fréquemment rapportée. Dans de très rares cas, des réactions anaphylactiques (œdème allergique, urticaire, érythème, collapsus, dyspnée, muqueuses pâles) peuvent se manifester. Des signes de léthargie, d'anorexie et d'ulcère ont été observés peu de temps après l'administration du produit et sont généralement disparus en moins de 24 heures, en l'absence de traitement ou une fois les causes sous-jacentes du vomissement corrigées.
Réactions observées depuis l'homologation : Les réactions indésirables survenues sont tirées de signalements concernant des réactions indésirables observées en pratique suite à l'injection de chlorure de maropitant. Toutes les réactions indésirables ne sont pas signalées et il n'est pas toujours possible d'établir avec certitude un lien de causalité entre l'exposition au médicament et les données de l'expérience. Les réactions indésirables signalées, énumérées par ordre décroissant de fréquence (sur système physiologique) :
• Site d'administration : douleur au point d'injection, œdème au point d'injection.
• Troubles généraux : léthargie, anorexie.
• Système immunitaire : œdème allergique, urticaire, anaphylaxie.
• Troubles cardiaques : collapsus, muqueuses pâles (pâleur).
• Système digestif : vomissement, hypersalivation, diarrhée.
• Peau et annexes cutanées : érythème, prurit.
• Troubles du comportement : vocalisation, hyperactivité.

PHARMACOLOGIE CLINIQUE :
Pharmacocinétique Emavert, une préparation à base de sulfobutylether-β-cyclodextrin (SBECD), une substance qui se lie plus fortement au maropitant à des températures plus basses, cette affinité accrue disparaît lorsque le produit se réchauffe. Par conséquent, bien que la vitesse initiale d'absorption systémique du produit, bien que la vitesse initiale d'absorption systémique du médicament puisse varier en fonction de la température du produit injecté, les changements d'affinité ne semblent pas influer sur l'exposition systémique au médicament lorsque celui-ci est administré en bolus intraveineux.
Chiens : Les paramètres pharmacocinétiques associés au maropitant après une dose unique par voie orale (PO), intraveineuse (IV) ou sous-cutanée (SC) à des beagles adultes sont présentés dans le tableau ci-dessous.
Paramètres pharmacocinétiques chez des beagles (moyenne ± ÉT ou moyenne et extrêmes)

Paramètre pharmacocinétique	SC à 1 mg/kg (n=8)	IV à 1 mg/kg (n=8)	PO à 2 mg/kg (n=8)	PO à 8 mg/kg (n=8)
$AUC_{0-\infty}$ (hr*ng/mL)	759.08±189.49	693.83±137.25	501±322	7840±5600
C_{max} (ng/mL)	122.99±46.06	296.62±60.77	81±32	776±604
$T_{1/2}$ (hr)	8.64* (6.15-20.48)	6.85* (4.87-11.30)	4.03 (2.48-7.09)	5.46 (3.39-7.65)
T_{max} (hr)	0.56±0.40	n/a	1.9±0.5	1.7±0.7

*Moyenne harmonique

La biodisponibilité du maropitant était beaucoup plus élevée après l'administration par voie sous-cutanée (91 % à la dose de 1 mg/kg) qu'après l'administration par voie orale (24 % à la dose de 2 mg/kg). Cela dit, la biodisponibilité orale pourrait être plus extrême en raison de la saturation du foie et du réticulum. Les chiens âgés d'un an ou plus tirent un bénéfice plus marqué de l'administration par voie intraveineuse. Bien que l'effet de premier passage hépatique contribue à la biodisponibilité relativement faible après une dose orale, le statut prandial ne modifie pas sensiblement l'ampleur de l'absorption orale. Une exposition plus forte que proportionnelle à la dose peut être anticipée si on augmente la dose (1-10 mg/kg PO). La clairance systémique du maropitant à la suite d'une injection intraveineuse de 1 mg/kg était de 149L/10 kg/h. Un taux d'accumulation de 1,5 a été observé après l'administration de maropitant, 1 fois par jour durant 5 jours consécutifs à 1 (SC) ou 2 (PO) mg/kg. La concentration maximale dans le plasma (C_{max}) et l'aire sous la courbe de la concentration plasmatique en fonction du temps ($AUC_{0-\infty}$) ont augmenté avec la dose administrée. Un chien a été identifié chez lui comme étant responsable du métabolisme du maropitant : le cytochrome P450 : les isoenzymes CYP2D15 et CYP3A12. D'après les données sur la pharmacocinétique in vitro de ces enzymes, on croit que la pharmacocinétique non linéaire du maropitant pourrait être en partie associée à la saturation de l'isoenzyme CYP2D15, une enzyme à faible capacité. Cependant, lorsque la dose augmente (20-80 mg/kg PO), la proportionnalité à la dose est rétablie. Toutefois d'après les données sur la pharmacocinétique in vitro, la participation de l'isoenzyme CYP3A12, une enzyme à capacité élevée, pourrait être partiellement associée à la saturation de l'isoenzyme CYP2D15 lorsque les doses augmentent (20-80 mg/kg).
Les différences de concentrations plasmatiques minimales observées au cours d'une seule dose portant à croire que l'exposition au maropitant des chiots âgés de 10 semaines pourrait être plus faible que celle des chiens adultes, en particulier après l'administration de doses de 1 ou 2 mg/kg.
Les paramètres pharmacocinétiques du maropitant après l'administration d