Cerenia® (maropitant citrate) Injectable

RIMADYL® (carprofen)

2022 Cerenia® (maropitant citrate) Injectable and Rimadyl® (carprofen) Injectable Pricing

2022 Cerenia and Rimadyl Price per 20 mL Bottle*:
Cerenia Injectable = $182.90 | Rimadyl Injectable = $143.10
Effective January 1, 2022

Weight (lb)	Cerenia Dose (mL)	Cerenia Cost*	Rimadyl Dose (mL)	Rimadyl Cost*	Total Cost
1	0.05	$0.46	0.04	$0.29	$0.74
2	0.09	$0.83	0.08	$0.57	$1.40
3	0.14	$1.25	0.12	$0.86	$2.11
4	0.18	$1.66	0.16	$1.14	$2.81
5	0.23	$2.08	0.20	$1.43	$3.51
6	0.27	$2.49	0.24	$1.72	$4.21
7	0.32	$2.91	0.28	$2.00	$4.91
8	0.36	$3.33	0.32	$2.29	$5.62
9	0.41	$3.74	0.36	$2.58	$6.32
10	0.45	$4.16	0.40	$2.86	$7.02
11	0.50	$4.57	0.44	$3.15	$7.72
12	0.55	$4.99	0.48	$3.43	$8.42
13	0.59	$5.40	0.52	$3.72	$9.12
14	0.64	$5.82	0.56	$4.01	$9.83
15	0.68	$6.24	0.60	$4.29	$10.53
16	0.73	$6.65	0.64	$4.58	$11.23
17	0.77	$7.07	0.68	$4.87	$11.93
18	0.82	$7.48	0.72	$5.15	$12.63
19	0.86	$7.90	0.76	$5.44	$13.34
20	0.91	$8.31	0.80	$5.72	$14.04
21	0.95	$8.73	0.84	$6.01	$14.74
22	1.00	$9.15	0.88	$6.30	$15.44
23	1.05	$9.56	0.92	$6.58	$16.14
24	1.09	$9.98	0.96	$6.87	$16.85
25	1.14	$10.39	1.00	$7.16	$17.55
26	1.18	$10.81	1.04	$7.44	$18.25
27	1.23	$11.22	1.08	$7.73	$18.95
28	1.27	$11.64	1.12	$8.01	$19.65
29	1.32	$12.05	1.16	$8.30	$20.35
30	1.36	$12.47	1.20	$8.59	$21.06
31	1.41	$12.89	1.24	$8.87	$21.76
32	1.45	$13.30	1.28	$9.16	$22.46
33	1.50	$13.72	1.32	$9.44	$23.16
34	1.55	$14.13	1.36	$9.73	$23.86
35	1.59	$14.55	1.40	$10.02	$24.57
36	1.64	$14.96	1.44	$10.30	$25.27
37	1.68	$15.38	1.48	$10.59	$25.97
38	1.73	$15.80	1.52	$10.88	$26.67
39	1.77	$16.21	1.56	$11.16	$27.37
40	1.82	$16.63	1.60	$11.45	$28.08
41	1.86	$17.04	1.64	$11.73	$28.78
42	1.91	$17.46	1.68	$12.02	$29.48
43	1.95	$17.87	1.72	$12.31	$30.18
44	2.00	$18.29	1.76	$12.59	$30.88
45	2.05	$18.71	1.80	$12.88	$31.58
46	2.09	$19.12	1.84	$13.17	$32.29
47	2.14	$19.54	1.88	$13.45	$32.99
48	2.18	$19.95	1.92	$13.74	$33.69
49	2.23	$20.37	1.96	$14.02	$34.39
50	2.27	$20.78	2.00	$14.31	$35.09

Weight (lb)	Cerenia Dose (mL)	Cerenia Cost*	Rimadyl Dose (mL)	Rimadyl Cost*	Total Cost
51	2.32	$21.20	2.04	$14.60	$35.80
52	2.36	$21.62	2.08	$14.88	$36.50
53	2.41	$22.03	2.12	$15.17	$37.20
54	2.45	$22.45	2.16	$15.45	$37.90
55	2.50	$22.86	2.20	$15.74	$38.60
56	2.55	$23.28	2.24	$16.03	$39.31
57	2.59	$23.69	2.28	$16.31	$40.01
58	2.64	$24.11	2.32	$16.60	$40.71
59	2.68	$24.53	2.36	$16.89	$41.41
60	2.73	$24.94	2.40	$17.17	$42.11
61	2.77	$25.36	2.44	$17.46	$42.81
62	2.82	$25.77	2.48	$17.74	$43.52
63	2.86	$26.19	2.52	$18.03	$44.22
64	2.91	$26.60	2.56	$18.32	$44.92
65	2.95	$27.02	2.60	$18.60	$45.62
66	3.00	$27.44	2.64	$18.89	$46.32
67	3.05	$27.85	2.68	$19.18	$47.03
68	3.09	$28.27	2.72	$19.46	$47.73
69	3.14	$28.68	2.76	$19.75	$48.43
70	3.18	$29.10	2.80	$20.03	$49.13
71	3.23	$29.51	2.84	$20.32	$49.83
72	3.27	$29.93	2.88	$20.61	$50.54
73	3.32	$30.34	2.92	$20.89	$51.24
74	3.36	$30.76	2.96	$21.18	$51.94
75	3.41	$31.18	3.00	$21.47	$52.64
76	3.45	$31.59	3.04	$21.75	$53.34
77	3.50	$32.01	3.08	$22.04	$54.04
78	3.55	$32.42	3.12	$22.32	$54.75
79	3.59	$32.84	3.16	$22.61	$55.45
80	3.64	$33.25	3.20	$22.90	$56.15
81	3.68	$33.67	3.24	$23.18	$56.85
82	3.73	$34.09	3.28	$23.47	$57.55
83	3.77	$34.50	3.32	$23.75	$58.26
84	3.82	$34.92	3.36	$24.04	$58.96
85	3.86	$35.33	3.40	$24.33	$59.66
86	3.91	$35.75	3.44	$24.61	$60.36
87	3.95	$36.16	3.48	$24.90	$61.06
88	4.00	$36.58	3.52	$25.19	$61.77
89	4.05	$37.00	3.56	$25.47	$62.47
90	4.09	$37.41	3.60	$25.76	$63.17
91	4.14	$37.83	3.64	$26.04	$63.87
92	4.18	$38.24	3.68	$26.33	$64.57
93	4.23	$38.66	3.72	$26.62	$65.28
94	4.27	$39.07	3.76	$26.90	$65.98
95	4.32	$39.49	3.80	$27.19	$66.68
96	4.36	$39.91	3.84	$27.48	$67.38
97	4.41	$40.32	3.88	$27.76	$68.08
98	4.45	$40.74	3.92	$28.05	$68.78
99	4.50	$41.15	3.96	$28.33	$69.49
100	4.55	$41.57	4.00	$28.62	$70.19

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 cats and 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.

IMPORTANT SAFETY INFORMATION: As a class, NSAIDs may be associated with gastrointestinal, kidney and liver side effects. These are usually mild, but may be serious. Pet owners should discontinue therapy and contact their veterinarian immediately if side effects occur. Evaluation for pre-existing conditions and regular monitoring are recommended for pets on any medication, including Rimadyl. Use with other NSAIDs or corticosteroids should be avoided. See full Prescribing Information, attached.

Zoetis representatives are not free to discuss resale prices with you. Only you can determine resale prices.

*Pricing only applies to list price and does not include buying groups/MZR.

zoetis

Cerenia®
(maropitant citrate)

Tablets and Injectable Solution

Antiemetic

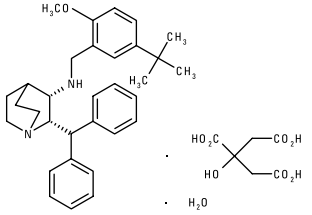
CERENIA Tablets
For oral use in dogs only

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_1) receptor antagonist that blocks the pharmacological action of substance P in the central nervous system (CNS). Maropitant is the non-proprietary designation for a substituted quinuclidine. The empirical formula is $C_{32}H_{40}N_2O \cdot C_6H_8O_7 \cdot H_2O$ and the molecular weight 678.81. The chemical name is (2*S*,3*S*)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate. Each 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.

DOSAGE 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/1 kg (1 mL/22 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 one time. 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[1]	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

[1] 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.

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[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
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

[1] The clinician observed and graded each cat's response to injection.
[2] Cat objected to the injection by retreating and vocalizing
[3] Cat objected to the injection by retreating, hissing, scratching, and vocalization

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 **DOSAGE AND ADMINISTRATION**).

Allergic reactions typically resolve with treatment within 48 hours after discontinuing CERENIA administration.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Vomiting is a complex process coordinated centrally by the emetic center which consists of several brainstem nuclei (area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus) that receive and integrate sensory stimuli from central and peripheral sources and chemical stimuli from the circulation and the cerebro-spinal fluid. Maropitant is a neurokinin 1 (NK_1) receptor antagonist which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. Substance P is found in significant concentrations in the nuclei comprising the emetic center and is considered the key neurotransmitter involved in emesis.[1] By inhibiting the binding of substance P within the emetic center, maropitant provides broad-spectrum effectiveness against neural (central) and humoral (peripheral) causes of vomiting. *In vivo* model studies in dogs have shown that maropitant has antiemetic effectiveness against both central and peripheral emetogens including apomorphine, and syrup of ipecac.

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

Pharmacokinetics (CERENIA 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[1]	8 mg/kg Single Dose	8 mg/kg repeat Doses[1]
T_{max}[2] (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_{max} (ng/mL)	154 (111)	304 (165)	588 (416)	1409 (516)
$AUC_{(0-24)}$ (ng*hr/mL)	1440 (982)	3890 (3030)	6730 (5030)	26600 (9200)
$T_{1/2}$[2] (hr)	NC	7.69 (6.21 - 17.8)	NC	25.4 (6.06 - 30.0)
Accumulation Ratio (R_{ac})[3]	NA	2.46 (1.68, 3.61)	NA	4.81 (3.28, 7.05)

[1]Following once daily doses of maropitant for 14 days.
[2]Median (Range)
[3]Ratio=Multiple Dose $AUC_{(0-24)}$/Single Dose $AUC_{(0-24)}$, Least square means (95% Confidence Interval)
NA= Not Applicable
NC= Not Calculated

Following oral administration, median time to reach Cmax 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 sulphobutylether-ß-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_{0-inf} (hr*ng/mL)	759.08±189.49	693.83±137.25	561±322	7840±5600
C_{max} (ng/mL)	102.99±46.06	296.62±60.77	81±32	776±604
$T_{1/2}$ (hr)	8.84[a] (6.15-20.48)	6.85[a] (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

[a] 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 $T_{1/2}$ seen after intravenous (IV) administration. Although hepatic first-pass metabolism contributed to the relatively low bioavailability after an oral dose, prandial status does not significantly affect the extent of oral bioavailability. Greater than dose-proportional drug exposure can be expected with an increase in dose (1–16 mg/kg PO). Systemic clearance of maropitant following IV administration was 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_{0-inf} (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)	6.57[a] (5.09-8.60)	4.86[a] (3.44-6.79)
T_{max} (hr)	0.43±0.33	n/a

[a] 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 (Vss) 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 feline isoforms involved in the hepatic biotransformation of maropitant. Renal and fecal clearances are minor routes of elimination for maropitant, with less than 1% of a 1 mg/kg 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 stimuli), 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 stimuli) 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	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 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 stimuli), vomiting was observed in 16.7% (2 of 12) of dogs treated with CERENIA Injectable Solution and 83.3% (10 of 12) of placebo-treated dogs. Following administration of syrup of ipecac (peripheral emetic stimuli) vomiting was observed in 25% (3 of 12) of dogs treated with CERENIA Injectable Solution and in 100% (12 of 12) of dogs treated with placebo.

In a study of veterinary cancer patients, dogs were treated with CERENIA Injectable Solution or placebo either 1 hour prior to cisplatin (prevention) or after the first vomiting episode following cisplatin (treatment) and monitored for 5 hours. In the groups evaluated for prevention of vomiting, 94.9% (37/39) of the dogs administered CERENIA Injectable Solution and 4.9% (2/41) of the dogs administered placebo did not vomit. In the groups evaluated for treatment, 21% (8/38) of the dogs administered CERENIA Injectable Solution and 5.1% (2/39) of the dogs administered placebo had no further episodes of vomiting following treatment.

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

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

*Dogs that exhibited an unacceptable level of vomiting (6 events) were withdrawn from the study and treated with another antiemetic.
**There were initially 41 and 42 dogs treated with either placebo or CERENIA Injectable Solution, respectively. However, if a dog did not vomit following cisplatin therapy, it did not receive a post-cisplatin treatment with either placebo or CERENIA 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_{last} and justification for the therapeutic equivalence of the IV and SC C_{max}.

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_{last} and justification for the therapeutic equivalence of the IV and SC C_{max}.

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 parvoviral 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 acclimatization period. Two dogs that received 8 mg/kg maropitant orally for 2 days were below the reference range for reticulocyte counts. Decreases in reticulocyte counts were also seen in 4 (of 8) placebo treated dogs (SC saline for 5 days). Hypocellular femoral bone marrow described as "minimal" was seen in 1 male that received 1 mg/kg maropitant SC for 5 days; reticulocyte counts were not available for this dog.

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 shorthair 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.

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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

8834091/4019387A&P

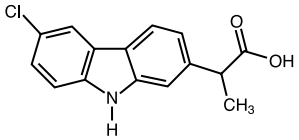
RIMADYL®

(carprofen)

Caplets/Chewable Tablets
For oral use in dogs only

Sterile Injectable Solution 50 mg/mL
For subcutaneous use in dogs only

Non-steroidal, anti-inflammatory drug



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

DESCRIPTION: Rimadyl (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen. Carprofen is the nonproprietary designation for a substituted carbazole, 6-chloro-α-methyl-9H-carbazole-2-acetic acid. The empirical formula is $C_{15}H_{12}ClNO_2$ and the molecular weight 273.72. The chemical structure of carprofen is shown above. Carprofen is a white, crystalline compound. It is freely soluble in ethanol, but practically insoluble in water at 25°C.

Rimadyl Injectable is a sterile solution containing carprofen. Each mL of Rimadyl Injectable contains 50.0 mg carprofen, 30.0 mg arginine, 88.5 mg glycocholic acid, 169.0 mg lecithin, 10.0 mg benzyl alcohol, 6.17 mg sodium hydroxide, with additional sodium hydroxide and hydrochloric acid as needed to adjust pH, and water for injection.

CLINICAL PHARMACOLOGY: Carprofen is a non-narcotic, non-steroidal anti-inflammatory agent with characteristic analgesic and antipyretic activity approximately equipotent to indomethacin in animal models.[1]

The mechanism of action of carprofen, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals.[2] The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity. The specificity of a particular NSAID for COX-2 versus COX-1 may vary from species to species.[3] In an *in vitro* study using canine cell cultures, carprofen demonstrated selective inhibition of COX-2 versus COX-1.[4] Clinical relevance of these data has not been shown. Carprofen has also been shown to inhibit the release of several prostaglandins in two inflammatory cell systems: rat polymorphonuclear leukocytes (PMN) and human rheumatoid synovial cells, indicating inhibition of acute (PMN system) and chronic (synovial cell system) inflammatory reactions.[1]

Several studies have demonstrated that carprofen has modulatory effects on both humoral and cellular immune responses.[5–9] Data also indicate that carprofen inhibits the production of osteoclast-activating factor (OAF), PGE_1, and PGE_2 by its inhibitory effects on prostaglandin biosynthesis.[1]

Based upon comparison with data obtained from intravenous administration, carprofen is rapidly and nearly completely absorbed (more than 90% bioavailable) when administered orally.[10] Peak blood plasma concentrations are achieved in 1–3 hours after oral administration of 1, 5, and 25 mg/kg to dogs. The mean terminal half-life of carprofen is approximately 8 hours (range 4.5–9.8 hours) after single oral doses varying from 1–35 mg/kg of body weight. After a 100 mg single intravenous bolus dose, the mean elimination half-life was approximately 11.7 hours in the dog. Rimadyl is more than 99% bound to plasma protein and exhibits a very small volume of distribution.

Comparison of a single 25 mg dose in Beagle dogs after subcutaneous and oral administration demonstrated that the dorsoscapular subcutaneous administration results in a slower rate of drug input (as reflected by mean peak observed concentrations) but comparable total drug absorption within a 12 hour dosing interval (as reflected by area under the curve from hours zero to 12 postdose).

Carprofen is eliminated in the dog primarily by biotransformation in the liver followed by rapid excretion of the resulting metabolites (the ester glucuronide of carprofen and the ether glucuronides of 2 phenolic metabolites, 7-hydroxy carprofen and 8-hydroxy carprofen) in the feces (70–80%) and urine (10–20%). Some enterohepatic circulation of the drug is observed.

INDICATIONS: Rimadyl is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

CONTRAINDICATIONS: Rimadyl should not be used in dogs exhibiting previous hypersensitivity to carprofen.

WARNINGS: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners, Adverse Reactions, Animal Safety and Post-Approval Experience).**

PRECAUTIONS: As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid.[11–14] When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients.[12,14] NSAID therapy could unmask occult disease which has previously been undiagnosed due to the absence of apparent clinical signs. Patients with underlying renal disease for example, may experience exacerbation or decompensation of their renal disease while on NSAID therapy.[11–14] The use of parenteral fluids during surgery should be considered to reduce the potential risk of renal complications when using NSAIDs perioperatively.

Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be approached cautiously, with appropriate monitoring. Concomitant use of Rimadyl with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Sensitivity to drug-associated adverse reactions varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Rimadyl treatment was not associated with renal toxicity or gastrointestinal ulceration in well-controlled safety studies of up to 10 times the dose in healthy dogs. As with any parenterally injected product, good hygienic procedures should be used when administering Rimadyl Injectable.

Rimadyl is not recommended for use in dogs with bleeding disorders (e.g., Von Willebrand's disease), as safety has not been established in dogs with these disorders. The safe use of Rimadyl in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established. Safety has not been established for IV or IM administration. Studies to determine the activity of Rimadyl when administered concomitantly with other protein-bound or similarly metabolized drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring additional therapy. Such drugs commonly used include cardiac, anticonvulsant and behavioral medications. It has been suggested that treatment with carprofen may reduce the level of inhalant anesthetics needed.[15] It is suggested to use different sites for additional injections. If additional pain medication is warranted after administration of the total daily dose of Rimadyl, alternative analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroids use to NSAID use.

Due to the palatable nature of Rimadyl chewable tablets, store out of reach of dogs in a secured location. Severe adverse reactions may occur if large quantities of tablets are ingested. If you suspect your dog has consumed Rimadyl chewable tablets above the labeled dose, please call your veterinarian for immediate assistance and notify Zoetis at 1-888-963-8471.

INFORMATION FOR DOG OWNERS:

Rimadyl, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes.

Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue Rimadyl therapy and contact their veterinarian immediately if signs of intolerance are observed.

The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

ADVERSE REACTIONS: During investigational studies for the caplet formulation with twice daily administration of 1 mg/lb, no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies (n=297) which were similar for carprofen caplet- and placebo-treated dogs. Incidences of the following were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%). The product vehicle served as control.

There were no serious adverse events reported during clinical field studies with once daily administration of 2 mg/lb. The following categories of abnormal health observations were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study (2 mg/lb once daily)

Observation	Rimadyl (n=129)	Placebo (n=132)
Inappetence	1.6	1.5
Vomiting	3.1	3.8
Diarrhea/Soft stool	3.1	4.5
Behavior change	0.8	0.8
Dermatitis	0.8	0.8
PU/PD	0.8	—
SAP increase	7.8	8.3
ALT increase	5.4	4.5
AST increase	2.3	0.8
BUN increase	3.1	1.5
Bilirubinuria	16.3	12.1
Ketonuria	14.7	9.1

Clinical pathology parameters listed represent reports of increases from pre-treatment values; medical judgment is necessary to determine clinical relevance.

During investigational studies of surgical pain for the caplet formulation, no clinically significant adverse reactions were reported. The product vehicle served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Surgical Pain Field Studies with Caplets (2 mg/lb once daily)

Observation*	Rimadyl (n=148)	Placebo (n=149)
Vomiting	10.1	13.4
Diarrhea/Soft stool	6.1	6.0
Ocular disease	2.7	0
Inappetence	1.4	0
Dermatitis/Skin lesion	2.0	1.3
Dysrhythmia	0.7	0
Apnea	1.4	0
Oral/Periodontal disease	1.4	0
Pyrexia	0.7	1.3
Urinary tract disease	1.4	1.3
Wound drainage	1.4	0

* A single dog may have experienced more than one occurrence of an event.

During investigational studies for the chewable tablet formulation, gastrointestinal signs were observed in some dogs. These signs included vomiting and soft stools.

There were no serious adverse events reported during clinical field studies for the injectable formulation. The following categories of abnormal health observations were reported. Saline served as control.

Percentage of Dogs with Abnormal Health Observations Reported in Clinical Field Study with the Injectable

Observation*	Rimadyl (n=168)	Placebo (n=163)
Vomiting	10.1	9.2
Diarrhea/soft stool	2.4	3.7
Dermatitis	0.6	1.2
Dysrhythmia	0.6	0.6
Swelling	0	1.2
Dehiscence	1.2	0
WBC increase	13.7	6.7

* A single dog may have experienced more than one occurrence of an event.

Post-Approval Experience:

Although not all adverse reactions are reported, the following adverse reactions are based on voluntary post-approval adverse drug experience reporting. The categories of adverse reactions are listed in decreasing order of frequency by body system.

Gastrointestinal: *Vomiting, diarrhea, constipation, inappetence, melena, hematemesis, gastrointestinal ulceration, gastrointestinal bleeding, pancreatitis.*

Hepatic: *Inappetence, vomiting, jaundice, acute hepatic toxicity, hepatic enzyme elevation, abnormal liver function test(s), hyperbilirubinemia, bilirubinuria, hypoalbuminemia. Approximately one-fourth of hepatic reports were in Labrador Retrievers.*

Neurologic: *Ataxia, paresis, paralysis, seizures, vestibular signs, disorientation.*

Urinary: *Hematuria, polyuria, polydipsia, urinary incontinence, urinary tract infection, azotemia, acute renal failure, tubular abnormalities including acute tubular necrosis, renal tubular acidosis, glucosuria.*

Behavioral: *Sedation, lethargy, hyperactivity, restlessness, aggressiveness.*

Hematologic: *Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, blood loss anemia, epistaxis.*

Dermatologic: *Pruritus, increased shedding, alopecia, pyotraumatic moist dermatitis (hot spots), necrotizing panniculitis/vasculitis, ventral ecchymosis.*

In rare situations, injection site reactions including necrosis, abscess and seroma formation, and granulomas have been reported with the injectable formulation.

Immunologic or hypersensitivity: *Facial swelling, hives, erythema.*

In rare situations, death has been associated with some of the adverse reactions listed above.

To report a suspected adverse reaction call 1-888-963-8471.

DOSAGE AND ADMINISTRATION: Always provide Client Information Sheet with prescription. Carefully consider the potential benefits and risk of Rimadyl and other treatment options before deciding to use Rimadyl. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage for oral administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. Rimadyl caplets and tablets are scored and dosage should be calculated in half-tablet increments. Tablets can be halved by placing the tablet on a hard surface and pressing down on both sides of the score. Rimadyl chewable tablets are palatable and willingly consumed by most dogs when offered by the owner. Therefore, they may be fed by hand or placed on food. Care should be taken to ensure that the dog consumes the complete dose.

The recommended dosage for subcutaneous administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total daily dose may be administered as either 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For control of post-operative pain, administer approximately 2 hours before the procedure.

PALATABILITY: A controlled palatability study was conducted which demonstrated that Rimadyl chewable tablets were readily accepted and consumed on first offering by a majority of dogs.

EFFECTIVENESS: Confirmation of the effectiveness of Rimadyl for the relief of pain and inflammation associated with osteoarthritis, and for the control of postoperative pain associated with soft tissue and orthopedic surgeries, was demonstrated in placebo-controlled, masked studies examining the anti-inflammatory and analgesic effectiveness of Rimadyl chewable tablets, caplets and injectable in various breeds of dogs.

Separate placebo-controlled, masked, multicenter field studies confirmed the anti-inflammatory and analgesic effectiveness of Rimadyl caplets when dosed at 2 mg/lb once daily or when divided and administered at 1 mg/lb twice daily. In these two field studies, dogs diagnosed with osteoarthritis showed statistically significant overall improvement based on lameness evaluations by the veterinarian and owner observations when administered Rimadyl at labeled doses.

Based upon the blood level comparison between subcutaneous and oral administration, Rimadyl effectiveness for osteoarthritis after dorsoscapular subcutaneous and oral administration should be similar, although there may be a slight delay in the onset of relief after subcutaneous injection.

Separate placebo-controlled, masked, multicenter field studies confirmed the effectiveness of Rimadyl caplets and injectable for the control of postoperative pain when dosed at 2 mg/lb once daily in various breeds of dogs. In these studies, dogs presented for ovariohysterectomy, cruciate repair and aural surgeries were administered Rimadyl preoperatively and for a maximum of 3 days (soft tissue) or 4 days (orthopedic) postoperatively. In general, dogs administered Rimadyl showed statistically significant reduction in pain scores compared to controls.

ANIMAL SAFETY: Laboratory studies in unanesthetized dogs and clinical field studies have demonstrated that Rimadyl is well tolerated in dogs after oral administration.

In target animal safety studies, Rimadyl was administered orally to healthy Beagle dogs at 1, 3, and 5 mg/lb twice daily (1, 3 and 5 times the recommended total daily dose) for 42 consecutive days with no significant adverse reactions. Serum albumin for a single female dog receiving 5 mg/lb twice daily decreased to 2.1 g/dL after 2 weeks of treatment, returned to the pre-treatment value (2.6 g/dL) after 4 weeks of treatment, and was 2.3 g/dL at the final 6-week evaluation. Over the 6-week treatment period, black or bloody stools were observed in 1 dog (1 incident) treated with 1 mg/lb twice daily and in 1 dog (2 incidents) treated with 3 mg/lb twice daily. Redness of the colonic mucosa was observed in 1 male that received 3 mg/lb twice daily.

Two of 8 dogs receiving 10 mg/lb orally twice daily (10 times the recommended total daily dose) for 14 days exhibited hypoalbuminemia. The mean albumin level in the dogs receiving this dose was lower (2.38 g/dL) than each of 2 placebo control groups (2.88 and 2.93 g/dL, respectively). Three incidents of black or bloody stool were observed in 1 dog. Five of 8 dogs exhibited reddened areas of duodenal mucosa on gross pathologic examination. Histologic examination of these areas revealed no evidence of ulceration, but did show minimal congestion of the lamina propria in 2 of the 5 dogs.

In separate safety studies lasting 13 and 52 weeks, respectively, dogs were administered orally up to 11.4 mg/lb/day (5.7 times the recommended total daily dose of 2 mg/lb) of carprofen. In both studies, the drug was well tolerated clinically by all of the animals. No gross or histologic changes were seen in any of the treated animals. In both studies, dogs receiving the highest doses had average increases in serum L-alanine aminotransferase (ALT) of approximately 20 IU.

In the 52-week study, minor dermatologic changes occurred in dogs in each of the treatment groups but not in the control dogs. The changes were described as slight redness or rash and were diagnosed as non-specific dermatitis. The possibility exists that these mild lesions were treatment related, but no dose relationship was observed.

Clinical field studies were conducted with 549 dogs of different breeds at the recommended oral doses for 14 days (297 dogs were included in a study evaluating 1 mg/lb twice daily and 252 dogs were included in a separate study evaluating 2 mg/lb once daily). In both studies the drug was clinically well tolerated and the incidence of clinical adverse reactions for Rimadyl-treated animals was no higher than placebo-treated animals (placebo contained inactive ingredients found in Rimadyl). For animals receiving 1 mg/lb twice daily, the mean post-treatment serum ALT values were 11 IU greater and 9 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. Differences were not statistically significant. For animals receiving 2 mg/lb once daily, the mean post-treatment serum ALT values were 4.5 IU greater and 0.9 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. In the latter study, 3 Rimadyl-treated dogs developed a 3-fold or greater increase in (ALT) and/or (AST) during the course of therapy. One placebo-treated dog had a greater than 2-fold increase in ALT. None of these animals showed clinical signs associated with laboratory value changes. Changes in the clinical laboratory values (hematology and clinical chemistry) were not considered clinically significant. The 1 mg/lb twice daily course of therapy was repeated as needed at 2-week intervals in 244 dogs, some for as long as 5 years.

Clinical field studies were conducted in 297 dogs of different breeds undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of Rimadyl 2 hours prior to surgery then once daily, as needed for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Rimadyl was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observation in Rimadyl- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in Rimadyl- and placebo-treated animals. Changes in clinicopathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 7.3 IU and 2.5 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. The mean post-treatment AST values were 3.1 IU less for dogs receiving Rimadyl and 0.2 IU greater for dogs receiving placebo.

Clinical field studies on the use of Rimadyl Injectable were conducted on 331 dogs undergoing orthopedic or soft tissue surgery. Dogs were administered 2 mg/lb of Rimadyl subcutaneously 2 hours prior to surgery and once daily thereafter, as needed, for 2 days (soft tissue surgery) or 3 days (orthopedic surgery). Rimadyl was well tolerated when used in conjunction with a variety of anesthetic-related drugs. The type and severity of abnormal health observations in Rimadyl- and placebo-treated animals were approximately equal and few in number (see Adverse Reactions). The most frequent abnormal health observation was vomiting and was observed at approximately the same frequency in Rimadyl- and placebo-treated animals. Changes in clinico-pathologic indices of hematopoietic, renal, hepatic, and clotting function were not clinically significant. The mean post-treatment serum ALT values were 8.4 IU and 7.0 IU less than pre-treatment values for dogs receiving Rimadyl and placebo, respectively. The mean post-treatment AST values were 1.5 IU and 0.7 IU greater for dogs receiving Rimadyl and placebo, respectively.

Swelling and warmth were associated with the injection site after subcutaneous administration of Rimadyl Injectable. These findings were not clinically significant. Long term use of the injectable has not been studied.

STORAGE: Store tablets at controlled room temperature 15°–30°C (59°–86°F). Store injectable under refrigeration 2°–8°C (36°–46°F). Once broached, product may be stored at temperatures up to 25°C (77°F) for 28 days.

HOW SUPPLIED: Rimadyl caplets and chewable tablets are scored, and contain 25 mg, 75 mg, or 100 mg of carprofen per caplet or tablet. Each caplet size is packaged in bottles containing 30, 60, or 180 caplets, or blister packs containing 4 caplets. Each chewable tablet size is packaged in bottles containing 7, 30, 60, or 180 tablets. Rimadyl Injectable is supplied in 20-mL, amber, glass, sterile, multi-dose vials.

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For a copy of the Safety Data Sheet (SDS) call 1-888-963-8471. To report adverse reactions call Zoetis Inc. at 1-888-963-8471.

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