

Librela[™]
(bedinvetmab injection)

GIVE DOGS MORE DAYS OF

PLAY



**Control canine osteoarthritis (OA)
pain with the first and only monthly
injectable anti-NGF monoclonal
antibody therapy for dogs**

NGF=nerve growth factor.

**A Veterinarian's Guide to Librela
and OA Pain Management**

Canine OA Pain Overview

Canine OA pain goes beyond the joint

- OA pain is a painful and chronic condition that can impact a dog's quality of life¹
- Dogs of all ages, sizes, and breeds can be affected²
- OA pain is underdiagnosed, leaving many dogs suffering unnecessarily
- Current OA pain treatment choices have limitations³



A new treatment option for canine OA pain could be a relief for dogs and owners because:

- Compliance is compromised if pet owners forget to administer treatment or if their dog is difficult to pill
- Middle-aged to senior dogs may have concurrent diseases that require additional medications
- Treatment administration may overwhelm pet owners, contributing to pet owner burden of care
- Not all dogs will respond to, and some may not tolerate, NSAID therapy

Did You Know?



Nearly **40%** of dogs show signs of OA pain,⁴ and nearly 25% are still undiagnosed⁵



Dogs with OA pain that are treated with NSAIDs only receive **~60.5** days of therapy annually⁶

Librela Is the First and Only Monthly Injectable Monoclonal Antibody Therapy for Dogs With OA Pain



Effectively controls canine OA pain with a monthly injection



Approved as safe and is metabolized and eliminated like naturally occurring antibodies with minimal involvement of the liver or kidneys⁷⁻⁹



Works differently than NSAIDs by reducing NGF effects, a key factor in canine OA pain¹⁰⁻¹²



Reduced canine OA pain, which led to increased activity and improved quality of life^{13-16*}

*Results from clinical studies conducted in the US and EU.^{15,16}
NGF=nerve growth factor;
NSAID=nonsteroidal anti-inflammatory drug.

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Librela Targets Canine OA Pain With a Unique Mechanism of Action

Librela is a monoclonal antibody (mAb) that reduces the actions of NGF, which include^{7,11,17}:

- ✓ Reducing canine OA pain
- ✓ Limiting the release of additional NGF and pro-inflammatory mediators
- ✓ Lowering neurogenic inflammation

Unlike daily oral pain medications used to treat OA pain and given by pet owners



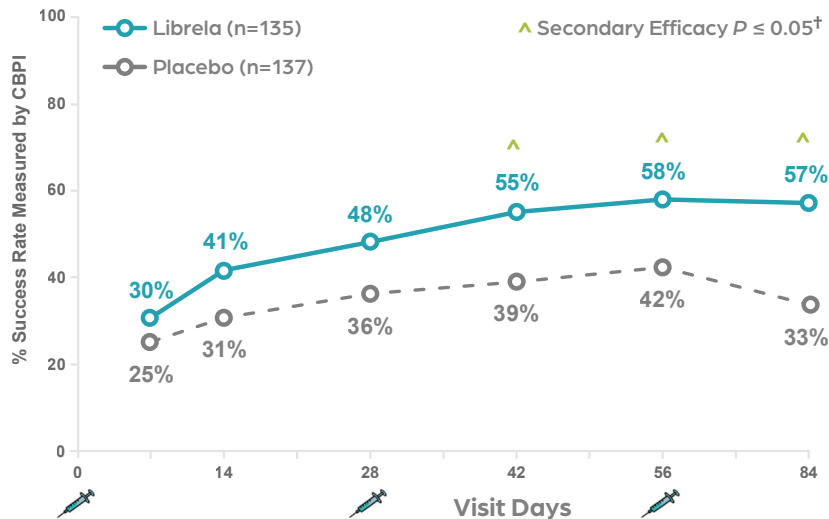
Librela is a monthly injection that provides long-lasting control of OA pain, administered by a veterinary professional

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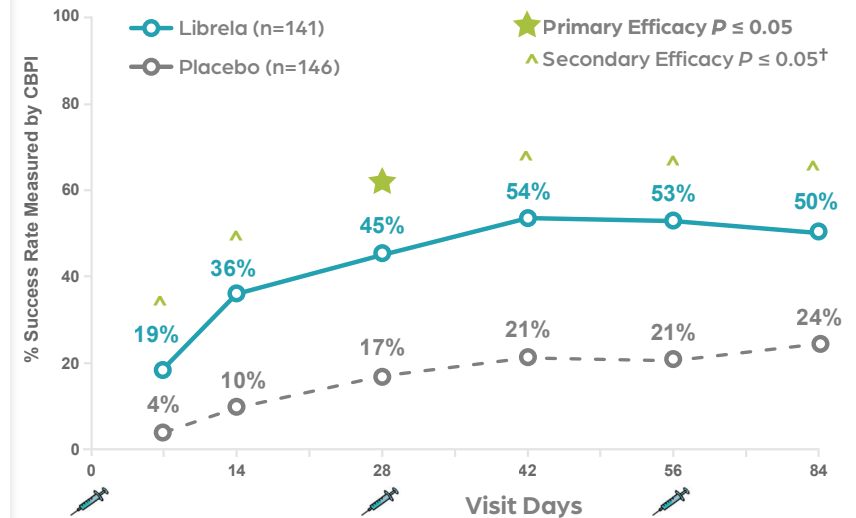
Reduced OA Pain Led to Improved Mobility

Librela was shown to reduce canine OA pain in clinical studies in the US and EU^{15,16*}

Librela Treatment Success: US 3-Month Clinical Study¹⁶



Librela Treatment Success: European 3-Month Clinical Study¹⁵



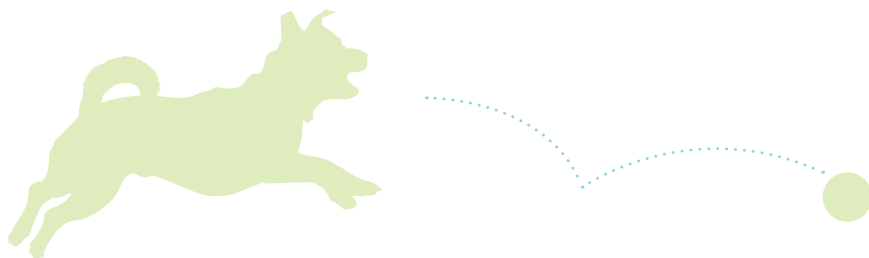
In both studies, day 28 was the prespecified primary effectiveness end point. The European study met statistical significance of difference in treatment success rate between treatment groups at Day 28; the US study did not.

Secondary end point P values are not adjusted for multiple testing; therefore, caution should be exercised in interpretation as there is potential for inflated Type I error and over-inferring the significance of treatment effect for these time points

Both studies used the Canine Brief Pain Inventory (CBPI), an owner-completed questionnaire designed to quantify the severity of OA pain and the impact of that pain on the activity of dogs. The CBPI is a clinically validated measurement that assesses pain severity, pain interference (activity), and overall quality of life.^{13,14}

The percentage of dogs considered treatment successes based on the owner CBPI assessment was greater in the Librela group compared to the control group for all assessments in both studies.

While effectiveness may not be seen until after the second dose of Librela, some dogs may experience a reduction in pain as early as 7 days after the first dose.

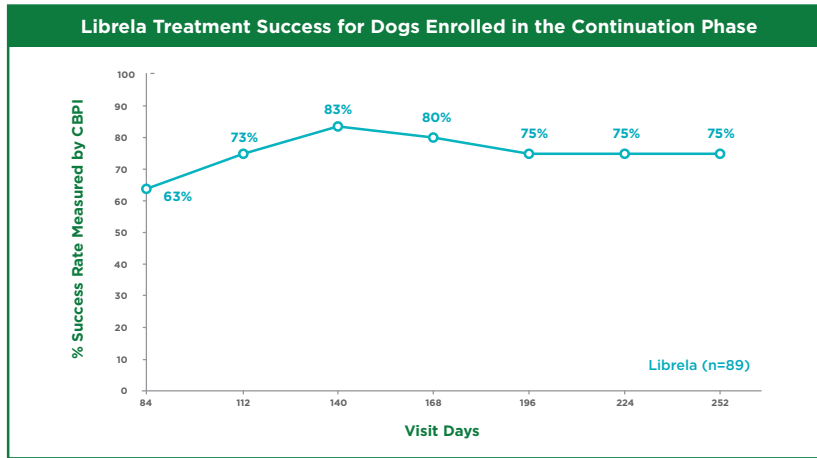


*A total of 559 dogs were enrolled in 2 clinical studies.

Librela Provided Continued Canine OA Pain Control With Monthly Injections¹⁵

The CBPI results showed that Librela improved the overall impression of the quality of life in dogs¹⁵

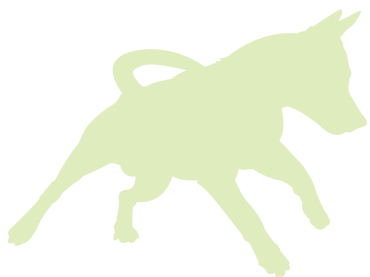
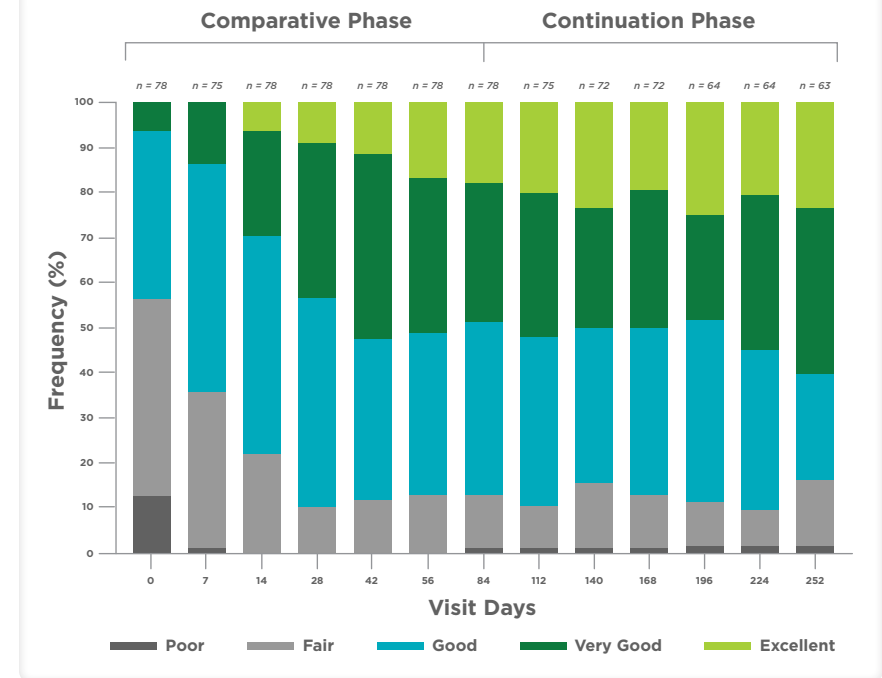
Librela Treatment Success for Dogs Enrolled in the Continuation Phase



89
DOGS

A total of 89 dogs that were considered treatment successes in the EU field study were enrolled in the continuation phase and were administered Librela monthly for an additional 6 months—a total of 9 months of treatment with Librela

Quality-of-Life Assessment for Dogs Enrolled in the Continuation Phase





Librela Is Approved as Safe and Effective⁷

Adverse events were similar to what would be expected for this population of dogs with OA^{7,15,16,18}

- In 2 clinical studies, adverse events for the 273 Librela-treated dogs were similar to what would be expected for this population of dogs with OA. The most common adverse events reported in those dogs were urinary tract infection, bacterial skin infection, and increased blood urea nitrogen*

Librela is a highly targeted monoclonal antibody^{8,9}

- It is eliminated via normal protein degradation pathways and has minimal metabolism by the liver or kidneys

Safety considerations

- In a study, Librela was well-tolerated at 10x the label dose^{19†}

*For the vast majority of dogs, an increase in BUN was not associated with clinical signs or changes in other renal parameters.

†Zoetis does not advise administering a higher dose than what is recommended by the label.

Librela Is Administered Subcutaneously Once a Month by Veterinary Professionals

The recommended dose of Librela is **0.23 mg/lb (0.5 mg/kg) body weight**

Weight	Librela Strength				
	5 mg/mL	10 mg/mL	15 mg/mL	20 mg/mL	30 mg/mL
11-22.1 lb (5-10 kg)	1 Vial				
22.2-44.1 lb (10.1-20 kg)		1 Vial			
44.2-66.1 lb (20.1-30 kg)			1 Vial		
66.2-88.2 lb (30.1-40 kg)				1 Vial	
88.3-132.3 lb (40.1-60 kg)					1 Vial
132.4-176.4 lb (60.1-80 kg)				2 Vials	
176.5-220.5 lb (80.1-100 kg)				1 Vial +	1 Vial
220.6-264.6 lb (100.1-120 kg)					2 Vials

For dogs <11 lb (<5 kg): Aseptically withdraw 0.045 mL/lb (0.1 mL/kg) from a 5 mg/mL vial into a single syringe and administer immediately. Discard the vial after the dose has been withdrawn.

For dogs ≥11 lb (≥5 kg): Dogs should be dosed by weight range according to the Librela dosing chart. Dogs are given the full content of 1 or 2 vials of the appropriate concentration based on body weight. Aseptically withdraw the total dose into a single syringe and administer immediately.

Librela should be stored in a refrigerator between 36 °F to 46 °F (2 °C to 8 °C). Do not freeze. Store vials in their boxes to protect from prolonged exposure to light.

Once punctured, contents of the vial should be used immediately, and any remaining solution should be discarded.

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Librela Frequently Asked Questions

1 What is Librela and how does it work?

Librela is the first and only monthly injectable anti-nerve growth factor (NGF) monoclonal antibody (mAb) therapy for the control of canine osteoarthritis (OA) pain. It works by reducing NGF effects, a key mediator in OA pain. By binding to NGF, Librela helps to reduce canine OA pain, limit the release of additional NGF and pro-inflammatory mediators, and lower neurogenic inflammation.^{10-12,17}

2 What is NGF?

Nerve growth factor, or NGF, is a signaling protein that is produced by injured tissues. NGF is necessary for the nervous system development in animals during growth, but once the nervous system is fully developed in an adult animal, NGF takes on a different function—one that plays an important role in initiating and perpetuating pain. Compared with healthy joints, dogs with OA have elevated NGF in the synovial fluid in their affected joints.^{10,20}

3 Is Librela safe?

Librela is approved as safe and effective.⁷ It is a highly targeted monoclonal antibody and is eliminated via normal protein degradation pathways with minimal metabolism by the liver or kidneys.^{8,9}

In clinical studies, adverse events were similar to what would be expected for the population of dogs with OA.¹⁸ The most common adverse events reported in the Librela-treated dogs in those studies were urinary tract infection, bacterial skin infection, dermatitis, and elevated blood urea nitrogen (BUN).^{*7,15,16}

Librela should not be administered to breeding, pregnant, or lactating dogs, or dogs with hypersensitivity or known allergy to bedinvetmab. Safety and effectiveness have not been evaluated in dogs under 12 months of age.

*For the vast majority of dogs, an increase in BUN was not associated with clinical signs or changes in other renal parameters.

4 How is Librela used and which pets can benefit from it?

Librela is specifically designed for long-term management of canine OA pain. It is an option for first-line canine OA pain management for most dogs that are 12 months of age or older with OA pain. Additional considerations when using Librela include:

- Dogs that will benefit from OA pain control with a monthly injection
- Pet owners who are not able to comply with administering oral medications and seek the ease of an in-clinic monthly injection
- Dogs that may be difficult to dose orally or need assured compliance
- Dogs that do not respond to or tolerate other OA pain medications

5 How effective is Librela and how long does it take for it to work?

In two field studies, dogs administered Librela as a monthly injection demonstrated a reduction in OA pain compared with dogs that received the placebo, and by reducing pain, Librela was shown to improve their mobility and overall quality of life.^{7,15,16}

While effectiveness may not be seen until after the second dose of Librela, some dogs may experience a reduction in pain as early as 7 days after the first dose. Additionally, in a continuation clinical study, dogs treated with Librela experienced lasting OA pain relief over the course of the study with monthly injections.^{15,16}

6 Can Librela be used with NSAIDs?

In a 2-week laboratory safety study, 8 dogs concurrently received 1 subcutaneous injection of Librela and 14 days of an injectable NSAID. Although there are no significant findings, this limited study did not provide sufficient data to support a conclusion on the safety of concurrent use of Librela and NSAIDs.^{7,19}

Librela Frequently Asked Questions (cont'd)

7 Can Librela be used with other commonly used medications?

In clinical studies, Librela was administered with commonly used medications, including parasiticides and antibiotics with no apparent drug interactions. Although a few dogs received vaccines and Librela concomitantly with no apparent drug interactions, interactions between Librela and vaccines have not been thoroughly evaluated.²¹⁻²³

8 How does Librela differ from Rimadyl® (carprofen)?

Both Librela and Rimadyl are approved for dogs with OA pain. Librela is an anti-NGF monoclonal antibody therapy specifically designed for long-term management of OA pain. It is administered as a subcutaneous injection once a month at the clinic by veterinary professionals. Please refer to the FDA-approved label for an understanding of the Librela mechanism of action.

Rimadyl is an NSAID that controls postoperative pain for soft tissue and orthopedic surgeries and provides relief from canine OA pain and inflammation. It is available in caplet, chewable, and injectable formulations for administration at the clinic or at home. Please refer to the FDA-approved label for an understanding of the Rimadyl mechanism of action.

9 Can pet owners give Librela at home?

Librela is a monthly injection only available by prescription from a licensed veterinarian because professional expertise is required to properly diagnose OA pain in dogs, administer the injection, reinforce the multi-modal management of osteoarthritis, look for concurrent problems, ensure proper administration and storage, and monitor the safe use of the product including treatment of any adverse reactions.

10 Is Librela available in other markets?

Yes, Librela received European Commission Marketing Authorization in November 2020, was approved for use in Canada in February 2021, and received approval in Australia and Japan in 2022. The medication has been used with success by veterinarians in the European Union and United Kingdom for more than 2 years, with 9 million doses distributed.²⁴



A Practical Approach to the Management of Canine OA Pain

Use these steps in your clinic to help you diagnose, treat, and monitor dogs with OA pain

Step 1: Screen all dogs ≥ 1 year of age for OA

A customer service representative can provide a screening tool like the Canine OA Checklist that you can use when the appointment is made or during the appointment. The vet tech or nurse will discuss results of the OA checklist with the owner.

Step 2: Confirm diagnosis

The veterinarian should observe the dog's movement and perform a physical and orthopedic exam. Additional diagnostics such as bloodwork or radiographs should be considered based on the patient.

Step 3: Implement a treatment plan

Once the diagnosis of OA and OA pain has been confirmed, implement a multimodal treatment plan. Start with analgesics, an appropriate diet and exercise plan, and evaluate ancillary treatment recommendations.

Step 4: Short-term follow-up

Before the owner leaves the clinic, set up their next visit. When starting a new treatment plan, it's always a good idea to follow up within the first week or two to ensure that they're following the plan. You can also answer questions or address any concerns they might have. Sending reminders for the next visit will help ensure compliance.

Step 5: Long-term monitoring

Your entire team will help you monitor your patient's long-term care, including routine rechecks, phone calls, prescription refills, and evaluating response and tolerance to treatment. Long-term monitoring allows you to adjust your treatment plan to ensure that the patient continues to receive optimal care.



Canine OA Pain Resources



LibrelaVetTeam.com

The official veterinary professional website for Librela. Learn more about the first injectable monoclonal antibody therapy to treat OA pain in dogs and get product updates.



Canine OA Pain Checklist

Use this checklist to help your clients understand the signs of canine OA pain so they're prepared to recognize it if their dog is suffering from OA pain.



Canine OA Exam Video Series

A series of short videos that demonstrate how to prepare for and complete a canine orthopedic exam.



Back-to-Play Guides

Help your clients learn about the phased approach to returning their dog back to play during treatment with Librela.



Before and After Videos

See how Librela has made a difference for real patients.



TheNewScienceofOAPain.com

A website dedicated to supporting the efforts of veterinary professionals that manage OA pain in both dogs and cats. Includes informative videos about the breakthrough anti-NGF therapeutic class, papers authored by key opinion leaders, the latest research in OA pain, and more.

IMPORTANT SAFETY INFORMATION FOR LIBRELA:

For use in dogs only. Women who are pregnant, trying to conceive or breastfeeding should take extreme care to avoid self-injection. Hypersensitivity reactions, including anaphylaxis, could potentially occur with self-injection. Librela should not be used in breeding, pregnant or lactating dogs. Librela should not be administered to dogs with known hypersensitivity to bedinvetmab. The most common adverse events reported in a clinical study were urinary tract infections, bacterial skin infections and dermatitis. See full Prescribing Information in the pocket.

IMPORTANT SAFETY INFORMATION FOR RIMADYL:

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 in the pocket.



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For more information about Librela,
contact your Sales Representative.
You can also find out more at
LibrelaVetTeam.com



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Librela™ (bedinvetmab injection)

Canine anti-nerve growth factor monoclonal antibody for subcutaneous use in dogs only.

Single-Use Vial

CAUTION

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

DESCRIPTION

LIBRELA (bedinvetmab injection) is a sterile injectable solution containing 5, 10, 15, 20, or 30 mg/mL of bedinvetmab in 20 mM histidine buffer pH 5.0 [(0.027% w/v L-histidine and 0.382% w/v histidine HCl monohydrate), 8.5% w/v trehalose dihydrate, 0.005% w/v disodium EDTA dihydrate, 0.01% w/v L-methionine, and 0.1% w/v poloxamer 188]. Bedinvetmab is a canine IgG monoclonal antibody (mAb), in which the variable regions from canine B cell sequence were joined with canine IgG constant sequences, and is expressed through recombinant DNA techniques in Chinese hamster ovary (CHO) cells. Bedinvetmab binds to nerve growth factor (NGF) to reduce NGF's effects. Such mAbs are commonly referred to as anti-NGF mAbs.

INDICATION

LIBRELA is indicated for the control of pain associated with osteoarthritis in dogs.

DOSE AND ADMINISTRATION

The minimum target dose of LIBRELA is 0.23 mg/lb (0.5 mg/kg) body weight, administered subcutaneously once a month. Dogs should be dosed by weight range according to the specific dosing information below.

The product does not contain a preservative. The full content of each vial is for single-use only. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

Dogs weighing ≥ 11 lb (≥ 5 kg):

Dogs should be dosed by weight range according to the Dosing Table below (Table 1). Dogs are given the full content of 1 or 2 vials of the appropriate concentration based on body weight. Aseptically withdraw the total dose into a single syringe and administer immediately.

Table 1. Dosing Table

Dog Body Weight in Pounds (lb)	Dog Body Weight in Kilograms (kg)	Number and Strength (mg/mL) of LIBRELA Vials to be Administered				
		5 mg/mL orange	10 mg/mL blue	15 mg/mL green	20 mg/mL gold	30 mg/mL purple
11-22.1	5-10	1 vial				
22.2-44.1	10.1-20		1 vial			
44.2-66.1	20.1-30			1 vial		
66.2-88.2	30.1-40				1 vial	
88.3-132.3	40.1-60					1 vial
132.4-176.4	60.1-80				2 vials	
176.5-220.5	80.1-100				1 vial	1 vial
220.6-264.6	100.1-120					2 vials

Dogs < 11 lb:

Aseptically withdraw 0.045 mL/lb (0.1 mL/kg) from a 5 mg/mL vial (orange vial) into a single syringe and administer immediately. Discard the vial after the dose has been withdrawn.

Effectiveness may not be achieved until after the second dose (see **EFFECTIVENESS**).

CONTRAINDICATIONS

LIBRELA should not be administered to dogs with known hypersensitivity to bedinvetmab.

LIBRELA should not be used in breeding dogs or in pregnant or lactating dogs. Immunoglobulin G class antibodies such as LIBRELA can pass through the placental blood barrier and be excreted in milk. Fetal abnormalities, increased rates of stillbirths and increased postpartum fetal mortality were noted in rodents and primates receiving anti-NGF monoclonal antibodies.

WARNINGS

User Safety Warnings

Not for use in humans. Keep this and all drugs out of reach of children. For use in dogs only.

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet, vial or carton to the physician.

Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.

The importance of Nerve Growth Factor in ensuring normal fetal nervous system development is well-established and laboratory studies conducted on nonhuman primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity.

PRECAUTIONS

Administration of monoclonal antibodies may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

The safe use of this product with other monoclonal antibodies has not been evaluated. Use with caution in dogs with known hypersensitivity to other immunoglobulin therapy.

Evaluations were not made to determine if interactions occurred between LIBRELA and veterinary vaccines.

Treatment with LIBRELA may result in the formation of anti-bedinvetmab antibodies and potentially the loss of product effectiveness (see **IMMUNOGENICITY**).

The safe use of anti-NGF monoclonal antibodies with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in dogs. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF monoclonal antibody. RPOA has not been characterized or reported in dogs.

The safety and effectiveness of LIBRELA has not been evaluated in dogs less than 12 months of age.

LIBRELA has not been studied in dogs that have a history of cruciate ligament rupture within six months before initial product use as these cases were excluded from the field studies.

Long term effects which may occur more than 9 months after the use of LIBRELA have not been evaluated.

NGF is expressed within the heart and vasculature, and the long-term effects of reduced NGF in dogs with cardiac disease are unknown.

Primates receiving high doses of anti-NGF monoclonal antibodies had anatomical changes in postganglionic cell bodies (reduced size and number of neurons). The change in cell body size returned to normal after anti-NGF monoclonal antibody administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of LIBRELA in young growing dogs.

ADVERSE REACTIONS

The safety of LIBRELA was assessed in a masked, controlled 84-day US field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 272 dogs, 135 dogs treated with LIBRELA and 137 dogs treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17 years old), weighed between 1.8 to 62.7 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 2 below.

Table 2. Number (%) of Dogs with Adverse Reactions Reported in the US Field Study

Adverse Reaction*	LIBRELA n (%) (Total N = 135)	Negative Control n (%) (Total N = 137)
Urinary tract infection	15 (11.1)	11 (8.0)
Bacterial skin infection	11 (8.1)	9 (6.6)
Dermatitis	10 (7.4)	8 (5.8)
Dermal mass	8 (5.9)	5 (3.6)
Erythema	6 (4.4)	5 (3.6)
Dermal cyst(s)	4 (3.0)	2 (1.5)
Pain on injection	4 (3.0)	2 (1.5)
Inappropriate urination**	4 (3.0)	1 (0.7)
Histiocytoma	3 (2.2)	0 (0.0)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Of these, two dogs treated with LIBRELA were among those reported with a urinary tract infection.

The safety of LIBRELA was also evaluated in a masked, controlled 84-day European field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 281 dogs, 138 dogs treated with LIBRELA and 143 treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17.5 years old), weighed between 1.7 to 66 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 3 below.

Table 3. Number (%) of dogs with Adverse Reactions Reported in the European Field Study

Adverse Event Reported*	LIBRELA n (%) (Total N = 138)	Negative Control n (%) (Total N = 143)
Increased Blood Urea Nitrogen (BUN)**	19 (13.8)	7 (4.9)
Lethargy	5 (3.6)	0 (0.0)
Emesis	4 (2.9)	1 (0.7)
Anorexia	3 (2.2)	0 (0.0)
Lameness	3 (2.2)	1 (0.7)
Cough	3 (2.2)	1 (0.7)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Two dogs treated with LIBRELA suffered serious adverse events and were euthanized during or after study completion: A 13-year old Bichon Frise had pre-existing increased urine protein-creatinine ratio and heart failure that worsened during study; the dog also had an increase in creatinine during the study and was diagnosed with renal failure and was euthanized 3 days after completing the study. An 8-year-old mixed breed dog had pancreatitis and was euthanized on Day 74. The remainder of the dogs that had elevations in the BUN did not have any obvious adverse events associated with this finding.

One dog in the LIBRELA group was diagnosed with pyelonephritis on Day 15; this dog had pre-existing increased serum BUN and creatinine and a recent history of urinary tract infection that was not confirmed resolved prior to enrollment. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were initiated on Day 7 for osteoarthritis-associated joint pain but NSAIDs were discontinued on Day 10 due to anorexia and gastroenteritis; azotemia worsened at Day 13 and the dog received no further LIBRELA treatment.

One dog in the LIBRELA group with a history of atopy, developed mild alopecia and mild erythema on the injection site on Days 5 and 23. Both episodes of alopecia and erythema resolved with treatment.

A total of 89 dogs were enrolled in a 6-month, single arm, open labeled, uncontrolled continuation of the EU field study and received monthly subcutaneous injections of LIBRELA. The study provided additional field safety information.

One dog experienced acute gastroenteritis and recovered following treatment for abdominal pain, fever, vomiting, and anorexia. One large breed dog enrolled for stiffl osteoarthritis developed acute forelimb lameness that was diagnosed as elbow dysplasia. Two dogs presented with rear limb paresis of unknown etiology, one of whom responded to ongoing NSAID treatment and one who did not.

CONTACT INFORMATION

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Zoetis Inc. at 1-888-963-8471.

For additional information about reporting adverse drug experience for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bedinvetmab is a recombinant canine monoclonal antibody that binds to nerve growth factor (NGF), reduces NGF binding to the tropomyosin receptor kinase A (TrkA) and p75 neurotrophin receptor (p75^{NTR}) receptors and decreases TrkA signal transduction in cell types involved in pain. *In vitro* binding studies suggest that bedinvetmab binds with high affinity to NGF but does not bind to other neurotrophins including human neurotrophin-3 (NT-3), canine and human NT-4, and human brain-derived neurotrophic factor (BDNF).

NGF has been found to be elevated in the osteoarthritic joints of dogs. Following a noxious stimulus, inflammatory cytokines and NGF are released by tissues of the joint.

NGF binds to TrkA/p75^{NTR} receptors found on peripheral nerves, immune cells, endothelial cells, synoviocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception. Bedinvetmab binds to NGF and prevents NGF/TrkA/p75^{NTR} cellular signaling. *In vitro* studies, bedinvetmab potentially inhibits NGF-mediated signaling as measured by a reduction in TF-1 cell proliferation and functionally blocks NGF-induced neurite outgrowth in rat PC-12 neuronal cells.

NGF binds to TrkA receptors located on immune cells to elicit the release of additional proinflammatory mediators, including NGF itself. These inflammatory mediators lead to further peripheral sensitization involved in pain perception. Bedinvetmab reduces the expression of these inflammatory mediators in rat PC-12 neuronal cells.

Pharmacokinetics

In a 6-month laboratory study of healthy, adult Beagles administered LIBRELA at monthly doses ranging from 1-10 mg/kg, the area under the curve (AUC) and the maximum concentration (C_{max}) increased nearly in proportion to dose and steady-state was achieved after approximately 2 doses. In a laboratory pharmacokinetic study in Beagles at 0.5-1.0 mg/kg, peak serum drug levels were observed at 4-7 days after subcutaneous dosing, the mean bioavailability relative to an intravenous dose was approximately 86%, and the elimination half-life was approximately 12 days.

In a field study at the labeled dose in dogs with osteoarthritis, the half-life was highly variable and averaged approximately 19 days (harmonic mean 15.8 days). Steady-state was achieved after 2 doses.

The metabolic pathway of bedinvetmab has not been characterized. As a canine IgG monoclonal antibody, bedinvetmab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

IMMUNOGENICITY

Antibodies binding to bedinvetmab (i.e., an anti-drug antibody, ADA), were detected using a multi-tiered ADA testing approach (screening, confirmatory, and titration). Testing the confirmed ADA samples for neutralizing activity of bedinvetmab was not performed. Due to limitations of the assay methods performed to evaluate immunogenicity (confirmatory and titration), clinically relevant conclusions or correlations were not determined from the immunogenicity data reported.

In the US Field Effectiveness Study, 267 of 272 enrolled dogs with osteoarthritis were evaluated for immunogenicity after receiving up to 3 doses of LIBRELA. The presence of pre-existing ADAs was confirmed in 5 out of 267 dogs; 4 dogs in the LIBRELA group and 1 dog in the control group. Three of these LIBRELA-treated dogs continued to have ADAs confirmed after treatment with LIBRELA. Of the remaining dogs evaluated for immunogenicity, the presence of ADAs was confirmed on Day 84 in 1 dog in the LIBRELA-treated group and 1 dog in the control group.

In the EU Field Effectiveness Study, 281 of 287 enrolled dogs with osteoarthritis were evaluated for immunogenicity after receiving up to 3 doses of LIBRELA. The presence of pre-existing ADAs was confirmed in 2 out of 281 dogs; both in the control group. Of the other 141 dogs in the control group, the presence of ADA was confirmed in 1 dog after receiving treatment with placebo (on Study Visit Day 56). Of the 138 LIBRELA-treated dogs, the presence of ADA was confirmed in 2 dogs after treatment with LIBRELA (1 dog on Study Visit Day 84 and 1 dog on Study Visit Study Day 28). Eighty-nine LIBRELA-treated dogs continued on with once monthly treatment for an additional six months, and 82 of these dogs were evaluated for immunogenicity after receiving up to 6 additional doses of LIBRELA. The presence of ADA was confirmed in an additional 2 dogs.

In the 6-Month Safety Study, the presence of ADAs was confirmed in 2 out of 8 negative control dogs and no ADAs were confirmed in any of the 24 dogs administered 7 doses of LIBRELA.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to LIBRELA with the incidence of antibodies to other products may not be appropriate.

EFFECTIVENESS

The overall evidence, based on the results of two field studies, supports the conclusion that LIBRELA is effective for the control of pain associated with osteoarthritis in dogs when given as a minimum of two doses administered one month apart.

A US field effectiveness study and a European (EU) field effectiveness study were conducted using a similar study design. Both studies included a group administered LIBRELA and a negative control group that was administered sterile saline. The primary effectiveness endpoint was treatment success (Yes/No) at Day 28 based on owner assessment of pain measured on the Canine Brief Pain Inventory (CBPI).^{1,2} CBPI treatment success was a secondary endpoint at Days 7, 14, 42, 56 and 84. Treatment success was defined as a reduction of ≥ 2 in Pain Interference Score (PIS) and ≥ 1 in Pain Severity Score (PSS) vs. Day 0. Dogs receiving rescue treatment (e.g., for lack of efficacy (LOE)) or withdrawn for LOE were counted as treatment failures starting on the day of rescue or withdrawal, respectively.

While the studies had similar success rates on Day 28 in the treatment groups administered LIBRELA (48% and 45.2%), the studies had differences in the success rates in the control groups. The success rate in the control group in the US study was 36.1% and the success rate of the control group in the EU study was 17.0%. Based on these results, there was a larger treatment effect size in the EU study as compared to the US study, such that the US study did not demonstrate a significant difference at Day 28. In the EU study, the primary effectiveness variable was successful and met statistical significance at Day 28 (P = 0.0018).

The CBPI data from both studies demonstrated a greater percentage of dogs achieving treatment success in the LIBRELA-treated vs. control groups at Day 42. This success rate was maintained with a third administration at Day 56 through the end of the study at Day 84. Taken together, the US and EU studies establish the effectiveness for LIBRELA (bedinvetmab injection) for the control of pain associated with osteoarthritis in dogs when given as a minimum of two doses administered one month apart.

US Field Effectiveness Study

An 84-day masked, randomized, controlled field study was conducted at 24 US veterinary clinics. The study enrolled 272 client-owned dogs with clinical signs of osteoarthritis confirmed by radiography and orthopedic examination. Enrolled dogs were randomized at an equal ratio into one of two treatment groups: LIBRELA (0.5 mg/kg, n = 135) or control (sterile saline, n = 137) and were treated on Days 0, 28, and 56. Dog age and body weight ranged from 1.0 to 17.0 years and 1.8 to 62.7 kg, respectively. The percentage of dogs considered treatment successes based on the owner CBPI assessment was greater in the LIBRELA-treated dogs compared to the control group for all assessments. The study failed to demonstrate statistical significance for effectiveness at Day 28; however, the difference in the percentage of treatment successes from Day 42 onward demonstrated a clinical effect in the LIBRELA group compared to the control group.

Table 4. Study #1: Least Squares Mean Percent Success by Assessment Day

Day	Group	N	% Success
7	LIBRELA	125	30.3
	Control	129	24.8
14	LIBRELA	129	41.4
	Control	130	30.5
28	LIBRELA	128	48.0
	Control	131	36.1
42	LIBRELA	121	54.8
	Control	126	38.9
56	LIBRELA	122	57.8
	Control	124	42.1
84	LIBRELA	118	57.1
	Control	118	33.4

EU Field Effectiveness Study

An 84-day masked, randomized, controlled field study was conducted at 26 different study sites located in Portugal, Hungary, Ireland and Germany. The study enrolled 287 client-owned dogs with clinical signs of osteoarthritis confirmed by radiography and orthopedic examination. Dogs were randomized at an equal ratio into one of two treatment groups: LIBRELA (0.5 mg/kg, n = 141) or control (sterile saline, n = 146) and

were treated on Days 0, 28, and 56. Dog age and body weight ranged from 1.0 to 17.5 years and 1.7 to 66.0 kg, respectively. The percentage of dogs considered treatment successes based on the owner CBPI assessment was greater for LIBRELA-treated dogs compared to the control group for all assessments. The study met statistical significance compared to the control at Day 28 (primary effectiveness endpoint; P = 0.0018). The difference in the percentage of treatment successes from Day 42 onward continued to demonstrate a clinical effect in the LIBRELA group compared to the control group.

Table 5. Study #2: Least Squares Mean Percent Success by Assessment Day

Day	Group	N	% Success
7	LIBRELA	128	18.5
	Control	130	4.0
14	LIBRELA	132	35.7
	Control	132	9.6
28	LIBRELA	131	45.2
	Control	131	17.0
42	LIBRELA	133	53.5
	Control	134	21.4
56	LIBRELA	133	52.9
	Control	134	20.6
84	LIBRELA	129	49.9
	Control	132	24.3

TARGET ANIMAL SAFETY

6 Month Margin of Safety Study:

LIBRELA (bedinvetmab injection) 15 mg/mL and 30 mg/mL concentrations were administered subcutaneously to 11 to 12-month old, healthy Beagles (8 dogs per group) at doses of 1 mg/kg (1X), 3 mg/kg (3X), and 10 mg/kg (10X) every 28 days for seven consecutive doses. The control group (8 dogs) received sterile saline injections. Dogs weighed 5.6-11.7 kg at study initiation.

There were no clinically significant changes noted in neurological examinations, body temperature, heart and respiratory rate, blood pressure, electrocardiography, and organ weights. Detailed pathology evaluation of the shoulder, elbow, hip, and knee joints were conducted.

Vomiting and soft stool were noted across all groups throughout the study. Scabbing on the face, neck and thorax was seen across all groups except the 1 mg/kg group. Injection site redness was noted sporadically for 1 control dog, 2 dogs in the 1 mg/kg treatment group, 5 dogs in the 3 mg/kg treatment group, and 5 dogs in the 10 mg/kg treatment group. One dog in the 3 mg/kg treatment group had a temporary, mild swollen facial area 26 days after the first dose that resolved spontaneously. Two dogs in the 3 mg/kg treatment group had lymphadenopathy on the last study day with no related histopathology findings. One dog in the 10 mg/kg treatment group had an approximately 2.5 cm X 3.5 cm circular raised firm erythematous lesion with slight serosanguinous discharge and mild scabs of the shaved cervical area that resolved over 14 days.

One dog in the 1 mg/kg treatment group had an increasing ALP value over the course of the study that increased threefold above the high end of the reference range at study completion. There was no gross or histopathology correlate.

One dog in the 1 mg/kg treatment group had mild cartilage necrosis in the left ulna and an erosion in the cartilage of the right ulna. One dog in the 3 mg/kg treatment group had mild bilateral, femoral neck enthesophytes observed on radiographs pre-treatment. On end of study radiography and pathology evaluation, this dog had an osteophyte of the left acetabulum, mild left acetabulum remodeling and severe left femoral neck enthesophytes. Microscopically, mild to moderate cartilage degeneration with erosion and proteoglycan depletion was also noted in the left proximal femur and acetabulum. The mild right femoral neck enthesophytes were the same grade as pre-treatment. The findings may be progression of an underlying musculoskeletal condition; however, a potential relation to treatment cannot be ruled out.

None of the LIBRELA-treated dogs developed anti-drug antibodies due to bedinvetmab administration.

Additional Safety Studies:

In a two-week laboratory safety study, eight dogs concurrently received one subcutaneous injection of LIBRELA at the high end of the inherent dose band (1 mg/kg) and fourteen days of an injectable NSAID. This limited laboratory study did not provide sufficient data to support a conclusion on the safety of concurrent use of LIBRELA and NSAIDs.

In a 3-month exploratory laboratory safety study using a non-final formulation of bedinvetmab administered by subcutaneous injection monthly for four doses, a dog administered a 4 mg/kg dose had a reddened and/or swollen muzzle abrasion, with an elevated white blood cell count, and elevated globulin level and fibrinogen level. At one of the injection administrations, one dog administered a 4 mg/kg dose had a 4 cm X 2 cm injection site erythema with an eschar that resolved; and one dog administered a 1 mg/kg dose had 3 cm X 1 cm injection site erythema that resolved. Another dog administered a 1 mg/kg dose had injection site erythema, scabbing, and mucopurulent discharge for 18 days.

STORAGE CONDITIONS

LIBRELA (bedinvetmab injection) should be stored in a refrigerator, 2° – 8°C (36° – 46° F). Do not freeze. Store vials in their boxes to protect from prolonged exposure to light. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

HOW SUPPLIED

LIBRELA is available in 5 strengths packaged in 4 mL glass vials containing an extractable volume of 1 mL of clear solution. Each strength is available in cartons containing 2 or 6 vials.

REFERENCES

- Brown DC, Bell M, Rhodes L. Power of treatment success definitions when the Canine Brief Pain Inventory is used to evaluate carprofen treatment for the control of pain and inflammation in dogs with osteoarthritis. *Amer J Vet Resch* 2013; 74(12):1467-1473.
- Brown DC, Bell M, Rhodes L. ERRATUM to: Power of treatment success definitions when the Canine Brief Pain Inventory is used to evaluate carprofen treatment for the control of pain and inflammation in dogs with osteoarthritis. *Amer J Vet Resch* 2014; 75(4):353.

Approved by FDA under NADA # 141-562

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007
March 2023

RIMADYL®

(carprofen)

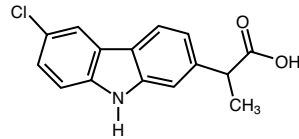
Caplets/Chewable Tablets

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), PGE₁, and PGE₂ 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 dorso-scapular 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)	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)	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	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.

DOSE 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 clinicopathologic 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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Approved by FDA under NADA #141-053, NADA #141-111, NADA #141-199



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Based on Rimadyl Caplets PI 40028070, Revised May 2019;
Rimadyl Chewable Tablets PI 40026875, Revised April 2019; and
Rimadyl Sterile Injectable Solution PI 4019448,
Revised March 2019.