



Elevating the Standard in Canine Osteoarthritis Care

Effectively control canine OA inflammation and pain with the precision power of Galliprant® (grapiprant tablets)

NSAID Use in Canine Osteoarthritis

Experts recommend prolonged daily NSAID therapy as the cornerstone of a multimodal approach to treating canine osteoarthritis.^{1,2} That's because NSAIDs treat both joint inflammation and the pain associated with OA, disrupting the progressive cycle of deterioration.

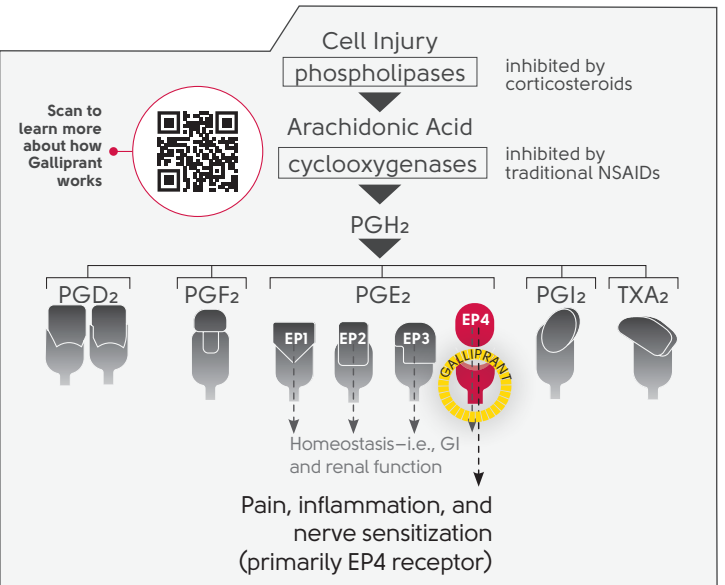
Galliprant features a unique mode of action that effectively addresses inflammation and pain while reducing the impact on organ health.

It selectively blocks sensitization (windup) and joint inflammation by blocking the EP4 receptor of PGE2.³

Minimum of three months of daily NSAID therapy is recommended at first diagnosis



- Even in **mild stages of OA**, a minimum of three months of daily NSAID therapy is recommended before determining if the dose can be tapered.
- Dogs with **moderate to severe OA** are likely to require ongoing daily dosing for the long term.

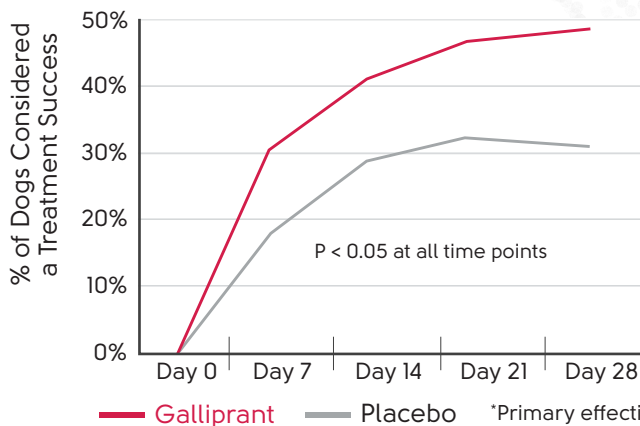


“In our practice, Galliprant is a first-line, long-term NSAID because it doesn't interfere with production of prostaglandins, and our considerable experience reflects its impressive safety data.”

Mark Epstein, DVM, DABVP Canine, DABVP Feline, CVPP, DAAPM

Galliprant is an ideal choice for long-term treatment because it works differently from other NSAIDs

Masked, randomized, placebo-controlled, multicenter field trial in 285 client-owned dogs⁴



Treatment Success: Improvement in pain severity score of 1 or more + improvement in pain interference score of 2 or more + overall assessment same or better

In a separate but similar study, **carprofen** showed a similar degree of efficacy⁵:

45.6% of treated dogs considered a success at Day 14 vs **23.7%** in the placebo group

In an Early Intervention Study, young dogs treated with Galliprant showed significant improvements in gait analysis, mobility, comfort, quality of life and sleep quality.⁶

Doges aged 9-48 months received Galliprant as part of a core multimodal approach that included an EPA-rich diet and exercise.

INDICATIONS: Galliprant is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

IMPORTANT SAFETY INFORMATION: For use in dogs only. Do not use in dogs that have a hypersensitivity to grapiprant. If Galliprant is used long term, appropriate monitoring is recommended. Concomitant use of Galliprant with other anti-inflammatory drugs, such as COX-inhibiting NSAIDs or corticosteroids, should be avoided. Concurrent use with other anti-inflammatory drugs or protein-bound drugs has not been studied.



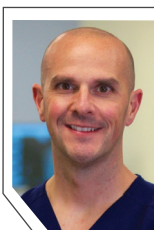
Galliprant doesn't just mask pain

It is specifically designed to treat joint inflammation and pain without tradeoffs

	Galliprant® (grapiprant tablets)	Rimadyl® (carprofen)	Previcox® (firocoxib)	Librela® (bedinvetmab)
FDA approved to control pain associated with canine OA	●	●	●	●
FDA approved to control inflammation associated with canine OA	●	●	●	
Does not disrupt production of prostaglandins important for organ health ^{3,4}	●			●
Safety of the label dose supported by a laboratory study in healthy dogs receiving up to ~15x the dose daily for 9 months*	●			
Stocked by more veterinary clinics in the U.S. than any other brand name NSAID ⁷	●			

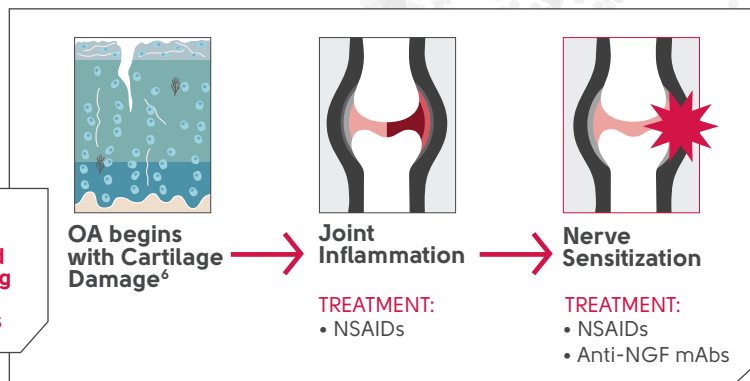
*No adverse event was serious enough to require removal from study. Treatment was associated with mild GI signs (soft stools with mucus and/or blood, vomiting) and mild, reversible decreases in total protein and albumin. There were no clinically significant changes in liver, kidney or coagulation parameters, or pathologic changes within the kidneys, liver or stomach.

NSAIDs treat pain and inflammation, while anti-NGF mAbs primarily treat pain^{1,2}



“We diagnose dogs with OA after joint pathology has occurred, so there is already a moderate to highly inflammatory state in the joint. This should be addressed with NSAIDs first before considering adjunctive therapies such as blocking nerve growth factor, which targets pain sensation but is not directly anti-inflammatory so is reserved for later stages of OA.”

David Dycus, DVM, MS, CCRP, DACVS



Treating Canine OA Shouldn't be a Pain

- Galliprant is safe, effective, and easily given from the comfort of home without injections.
- It's a once-a-day, flavored chewable tablet that fits into your clients' daily routines.

See how a targeted approach to treating canine OA works by visiting my.elanco.com/us/galliprant



IMPORTANT SAFETY INFORMATION: The safe use of Galliprant has not been evaluated in dogs younger than 9 months of age and less than 8 lbs (3.6 kg), dogs used for breeding, pregnant or lactating dogs, or dogs with cardiac disease. The most common adverse reactions were vomiting, diarrhea, decreased appetite, and lethargy. See accompanying product label for complete safety information.

References:

- Cachon T, Frykman O, Innes JF, Lascelles BD, Okumura M, Sousa P, Staffieri F, Steagall PV, Van Ryssen B. COAST Development Group's international consensus guidelines for the treatment of canine osteoarthritis. *Frontiers in Veterinary Science*. 2023 Aug 3;10:1137888.
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- Kirkby Shaw K, Rausch-Derra LC, Rhodes L. Grapiprant: an EP4 prostaglandin receptor antagonist and novel therapy for pain and inflammation. *Vet Med Sci*. 2016;2(1):3-9
- Rausch-Derra L, Huebner M, Wofford J, Rhodes L. 2016. "A Prospective, Randomized, Masked, Placebo-Controlled Multisite Clinical Study of Grapiprant, an EP4 Prostaglandin Receptor Antagonist (PRA), in Dogs with Osteoarthritis." *J Vet Intern Med*, 30.3: 756–763.
- 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. *American Journal of Veterinary Research*. 2013 Dec 1;74(12):1467-73.
- Enomoto M 51st Veterinary Orthopedic Society Conference, Feb 10-17 2024, Elanco approved abstract materials.
- Elanco Animal Health. Market data on file.

NSAID: Non-steroidal anti-inflammatory drug; NGF: nerve growth factor; mAbs: monoclonal antibodies

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Elanco

TM

Galliprant[®]

(grapiprant tablets)

For oral use in dogs only

20 mg, 60 mg and 100 mg flavored tablets

A prostaglandin E₂ (PGE₂) EP4 receptor antagonist; a non-cyclooxygenase inhibiting, non-steroidal anti-inflammatory drug

Caution:

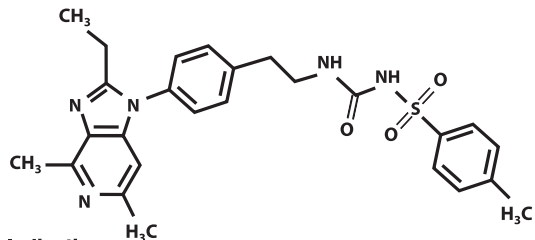
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

GALLIPRANT (grapiprant tablets) is a prostaglandin E₂ (PGE₂) EP4 receptor antagonist; a non-cyclooxygenase (COX) inhibiting, non-steroidal anti-inflammatory drug (NSAID) in the piroprant class. GALLIPRANT is a flavored, oval, biconvex, beige to brown in color, scored tablet debossed with a "G" that contains grapiprant and desiccated pork liver as the flavoring agent.

The molecular weight of grapiprant is 491.61 Daltons. The empirical formula is C₂₆H₂₉N₅O₃S. Grapiprant is N-[[[2-[4-(2-Ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl]amino]carbonyl]-4-methylbenzenesulfonamide.

The structural formula is:



Indication:

GALLIPRANT (grapiprant tablets) is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Dosage and Administration:

Always provide "Information for Dog Owners" Sheet with prescription.

Use the lowest effective dose for the shortest duration consistent with individual response.

The dose of GALLIPRANT (grapiprant tablets) is 0.9 mg/lb (2 mg/kg) once daily.

Only the 20 mg and 60 mg tablets of GALLIPRANT are scored.

The dosage should be calculated in half tablet increments.

Dogs less than 8 lbs. (3.6 kgs) cannot be accurately dosed.

Dosing Chart

Dose	Weight in pounds	Weight in kilograms	20 mg tablet	60 mg tablet	100 mg tablet
0.9 mg/lb (2 mg/kg) once daily	8-15	3.6-6.8	0.5		
	15.1-30	6.9-13.6	1		
	30.1-45	13.7-20.4		0.5	
	45.1-75	20.5-34		1	
	75.1-150	34.1-68			1

The 100 mg tablet is not scored and should not be broken in half.

Breaking the 100 mg tablet in half will not guarantee that half of the active ingredient is contained within each half of the tablet. For dogs larger than 150 lbs (68 kgs), use a combination of tablet and half tablets to achieve the appropriate dose.

Contraindications:

GALLIPRANT should not be used in dogs that have a hypersensitivity to grapiprant.

Warnings:

Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans.

For use in dogs only. Store GALLIPRANT out of reach of dogs and other pets in a secured location in order to prevent accidental ingestion or overdose.

PA103754X

Precautions:

The safe use of GALLIPRANT has not been evaluated in dogs younger than 9 months of age and less than 8 lbs (3.6 kg), dogs used for breeding, or in pregnant or lactating dogs.

Adverse reactions in dogs receiving GALLIPRANT may include vomiting, diarrhea, decreased appetite, mucoid, watery or bloody stools, and decreases in serum albumin and total protein.

If GALLIPRANT is used long term appropriate monitoring is recommended.

Concurrent use with other anti-inflammatory drugs has not been studied.

Concomitant use of GALLIPRANT with other anti-inflammatory drugs, such as COX-inhibiting NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after a daily dose of GALLIPRANT, a non-NSAID/non-corticosteroid class of analgesic may be necessary.

The concomitant use of protein-bound drugs with GALLIPRANT has not been studied. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications.

Drug compatibility should be monitored in patients requiring adjunctive therapy. Consider appropriate washout times when switching from one anti-inflammatory drug to another or when switching from corticosteroids or COX-inhibiting NSAIDs to GALLIPRANT use.

The use of GALLIPRANT in dogs with cardiac disease has not been studied.

It is not known whether dogs with a history of hypersensitivity to sulfonamide drugs will exhibit hypersensitivity to GALLIPRANT. GALLIPRANT is a methylbenzenesulfonamide.

Adverse Reactions:

In a controlled field study, 285 dogs were evaluated for safety when given either GALLIPRANT or a vehicle control (tablet minus grapiprant) at a dose of 2 mg/kg (0.9 mg/lb) once daily for 28 days. GALLIPRANT-treated dogs ranged in age from 2 yrs to 16.75 years. The following adverse reactions were observed:

Table 1. Adverse reactions reported in the field study.

Adverse reaction*	GALLIPRANT (grapiprant tablets) N = 141	Vehicle control (tablets minus grapiprant) N = 144
Vomiting	24	9
Diarrhea, soft stool	17	13
Anorexia, inappetence	9	7
Lethargy	6	2
Buccal ulcer	1	0
Immune mediated hemolytic anemia	1	0

*Dogs may have experienced more than one type or occurrence during the study.

GALLIPRANT was used safely during the field studies with other concurrent therapies, including antibiotics, parasiticides and vaccinations.

To report suspected adverse drug events and/or to obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, call 1-888-545-5973.

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>

Information for Dog Owners:

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 vomiting, diarrhea, decreased appetite, and decreasing albumin and total protein. Appetite and stools should be monitored and owners should be advised to consult with their veterinarian if appetite decreases or stools become abnormal.

Clinical Pharmacology:

Grapiprant is a prostaglandin E₂ (PGE₂) EP4 receptor antagonist; a non-cyclooxygenase inhibiting, non-steroidal, anti-inflammatory drug. Grapiprant has a canine EP4 receptor binding affinity (K_i) of 24 nM.

Prostaglandins have a wide variety of physiologic effects. Prostaglandin E₂ (PGE₂) is a prostanoid that exerts its effects via four receptors, EP1, EP2, EP3, and EP4. PGE₂ is involved in mediating inflammatory pain, vasodilation, increasing vascular permeability; as well as gastrointestinal homeostasis, renal function and

reproductive functions. The EP4 receptor is important in mediating pain and inflammation as it is the primary mediator of the PGE₂-elicited sensitization of sensory neurons¹ and PGE₂-elicited inflammation.² Grapiprant blocks PGE₂-elicited pain and inflammation by antagonizing the EP4 receptor.

The EP4 receptor, along with the EP1, EP2 and EP3 receptors, is involved in PGE₂ mediated effects on gastrointestinal homeostasis and renal function. PGE₂ effects mediated solely by the EP4 receptor are stimulation of mucus secretion in the stomach and large intestine, stimulation of acid secretion in the stomach, inhibition of small intestine motility and inhibition of cytokine expression in the large intestine.³ While PGE₂ gastroprotective action is mediated by EP1, the healing-promoting action of PGE₂ in the stomach is mediated by the EP4 receptor.⁴ In the kidney, the PGE₂ antinatriuretic effect is mediated by the EP4 receptor.⁵

EP4 receptors are abundantly expressed in the heart of dogs,⁶ the clinical relevance of which is unknown. The EP4 receptor is not involved in generation of pyrexia.

Grapiprant is not a potential inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 mediated metabolism pathways. Grapiprant is a substrate of P-glycoprotein transport. *In vitro* metabolism with dog liver microsomes identified two oxidative metabolites, M3 (hydroxyl) and M5 (N-dealkylation).

The pharmacokinetic characterization of grapiprant following oral administration of GALLIPRANT tablets to healthy Beagles is provided in the table below.

Table 2. Mean (±SD) Plasma Pharmacokinetic Parameters for Grapiprant in Beagles after single oral dose of GALLIPRANT tablet formulation

Study	Study 1 ¹	Study 1 ¹	Study 2 ²	Study 2 ²
PK Parameter	2 mg/kg (n = 10) (Fasted)	2 mg/kg (n = 10) (Fed)	6 mg/kg (n = 8) (Fasted)	50 mg/kg (n = 8) (Fasted)
Tmax ³ (hr)	1.0 (0.5 – 1.03)	1.0 (0.5 – 8.07)	1.0 (1.0 – 2.0)	2.0 (1.0 – 4.0)
Cmax (ng/mL)	1210 (341)	278 (179)	5720 (3220)	98500 (13100)
AUC(0-inf) (ng*hr/mL)	2790 (982)	1200 (523)	17800 (5520)	414000 (73700)
T1/2 (hr)	4.60 (4.19)	5.67 (3.27)	5.01 (1.95)	5.21 (1.66)
Fed/Fasted Relative Bioavailability Geometric Mean Ratio of AUC (90% Confidence Limits)	0.37 (0.28 – 0.46)		NA	

¹Study 1 was a food effect determination study.

²Study 2 was a PK bridging study conducted using 60 mg GALLIPRANT tablets at 6 mg/kg dose and 5 X 100 mg GALLIPRANT tablets at 50 mg/kg dose.

³Median (Range)

Grapiprant is absorbed rapidly following an oral dose of the GALLIPRANT; with Cmax values achieved within approximately 2 hr post-dose (Tmax). Intake of the tablet with food significantly reduces the oral bioavailability, with mean Cmax and AUC grapiprant values reduced 4-fold and 2-fold, respectively. The systemic grapiprant exposure increases in a greater than dose proportional manner.

The mean terminal elimination half-life (T1/2) ranges between 4.60 to 5.67 hr.

Following once daily dosing, negligible drug accumulation in the blood is anticipated. Following an oral dose of radiolabeled grapiprant to dogs, the majority of the dose was excreted within the first 72 hr (84%) and approximately 88.7% of the dose was excreted in 192 hr. In a bile duct cannulated dog study, approximately 55.6%, 15.1% and 19.1% of the dose was excreted in bile, urine and feces, respectively, suggesting the high oral bioavailability of grapiprant in dogs (> 70%). Four metabolites were identified; two hydroxylated metabolites, one N-deamination metabolite (major metabolite urine (3.4%) and feces (7.2%)) and one N-oxidation metabolite. Metabolite activity is not known. Plasma protein binding of grapiprant was ~95%.

Effectiveness:

Two hundred and eighty five (285) client-owned dogs were enrolled in the study and evaluated for field safety. GALLIPRANT-treated dogs ranging in age from 2 to 16.75 years and weighing between 4.1 and 59.6 kgs (9 – 131 lbs) with radiographic and clinical signs of osteoarthritis were enrolled in a placebo-controlled, masked field study. Dogs had a 7-day washout from NSAID or other current OA therapy.

Two hundred and sixty two (262) of the 285 dogs were included in the effectiveness evaluation. Dogs were assessed for improvements in pain and function by the owners using the Canine Brief Pain Inventory (CBPI) scoring system.⁷ A statistically significant difference in the proportion of treatment successes in the GALLIPRANT group (63/131 or 48.1%) was observed compared to the vehicle control group (41/131 or 31.3%). GALLIPRANT demonstrated statistically significant differences in owner assessed pain and function. The results of the field study demonstrate that GALLIPRANT, administered at 2 mg/kg (0.9 mg/pound) once daily for 28 days, was effective for the control of pain and inflammation associated with osteoarthritis.

Animal Safety:

In a 9-month toxicity study, grapiprant in a methylcellulose suspension was administered by oral gavage once daily to healthy Beagles at doses of 1, 6, and 50 mg/kg/day. Based on a relative bioavailability study comparing grapiprant in methylcellulose suspension to GALLIPRANT tablets, the corresponding equivalent doses were 0.75 mg/kg (0.12X – 0.25X), 4.44 mg/kg (0.72X – 1.48X) and 30.47 mg/kg (4.88X – 10.16X) of the GALLIPRANT tablets. Four animals/sex were used in each dose group and 2 additional animals/sex were used in the 50 mg/kg dose group to evaluate recovery after drug cessation. Vomiting and soft-formed or mucus stool were observed in all groups, including controls, with higher incidence in grapiprant-treated dogs. Decreases in serum albumin and total protein were seen with increasing doses of grapiprant. Hypoalbuminemia and hypoproteinemia were reversible when treatment was discontinued. Three treated dogs and one control dog had elevated alkaline phosphatase values. One animal in the 50 mg/kg group (equivalent to 30.47 mg/kg of tablet formulation) had mild regeneration of the mucosal epithelium of the ileum.

In a field study conducted in 366 client-owned dogs to evaluate GALLIPRANT at doses of 2 mg/kg once daily, 5 mg/kg once daily, 4 mg/kg twice daily, or placebo twice daily, the most common adverse reactions related to treatment were diarrhea, vomiting and inappetence. Changes in clinical pathology included concurrent elevations of alkaline phosphatase and alanine aminotransferase values on Day 28, and dose-dependent decreases in total protein values. There was no clinical impact related to these clinical pathology changes.

Storage Conditions:

Store at or below 86° F (30° C)

How Supplied:

20 mg, 60 mg and 100 mg flavored tablets in 7, 30 and 90 count bottles

Approved by FDA under NADA # 141-455

Manufactured for:

Elanco US Inc.
Greenfield, IN 46140

References:

1. Nakao, K., Murase, A., et al. CJ-023,423, a novel, potent and selective prostaglandin EP4 receptor antagonist with antihyperalgesic properties. *The Journal of Pharmacology and Experimental Therapeutics*. 2007; 322(2), 686-694.
2. Murase, A., Okumura, T., et al. Effect of prostanoid EP4 receptor antagonist, CJ-042,794, in rat models of pain and inflammation. *European Journal of Pharmacology*. 2008; 580(1-2), 116-121.
3. Takeuchi, K., S. Kato, et al. Prostaglandin EP receptors involved in modulating gastrointestinal mucosal integrity. *Journal of Pharmacological Sciences*. 2010; 114(3): 248-261.
4. Hatazawa R, Tanaka A, Tanigami M, et al. Cyclooxygenase-2/prostaglandin E₂ accelerates the healing of gastric ulcers via EP4 receptors. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2007; 293: G788-G797.
5. Nasrallah R, Hassouneh R, and Hebert R. Chronic kidney disease: targeting prostaglandin E₂ receptors. *American Journal of Physiology Renal Physiology*. 2014; 307: F242-250.
6. Castleberry TA, Lu B, et al. Molecular cloning and functional characterization of the canine prostaglandin E₂ receptor EP4 subtype. *Prostaglandins and Other Lipid Mediators*. 2001; 65: 167-187.
7. http://www.vet.upenn.edu/docs/default-source/VIC/canine-bpi_userguide.pdf?sfvrsn=0

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