



Controlling inflammation is critical to managing canine osteoarthritis (OA).^{1,2,3}

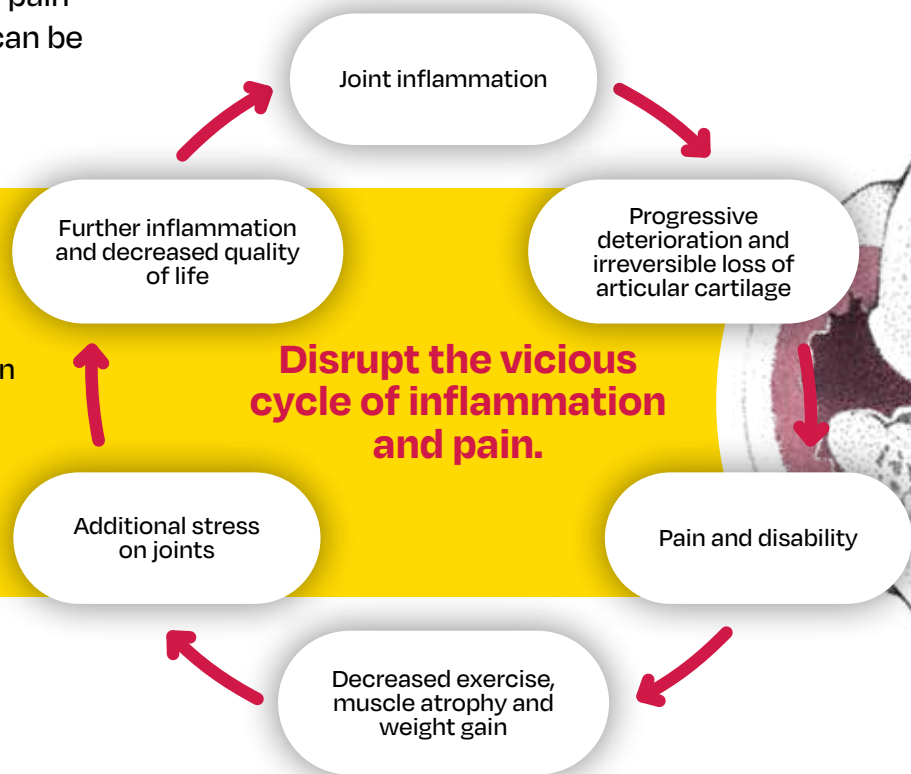
Why Galliprant® (grapiprant tablets) is a first-line choice for canine OA treatment.

OA is a disease of inflammation.

- Inflammatory mediators (e.g., PGE₂, IL-1) play a pivotal role in OA pathogenesis and disease progression.
- Increased PGE₂ in the joint leads to sensitization, or windup, and can lead to heightened pain sensation and chronic pain, which can be difficult to treat.

NSAIDs are the cornerstone of OA treatment.

Because they manage both inflammation and pain, NSAIDs have historically been, and currently remain an effective treatment option. **But not all NSAIDs are the same.**



INDICATION

Galliprant is an NSAID that controls pain and inflammation associated with osteoarthritis in dogs.

IMPORTANT SAFETY INFORMATION

Not for use in humans. For use in dogs only. Keep this and all medications out of reach of children and pets. Store out of reach of dogs and other pets in a secured location in order to prevent accidental ingestion or overdose. 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. 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. For full prescribing information see Galliprant package insert.

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Recognize the source of OA pain in dogs and the treatment becomes clear.

Galliprant® (grapiprant tablets) is an NSAID that is specifically designed to manage OA by effectively treating **both inflammation and pain** without trade-offs.



Scan to learn more about how Galliprant works

	Galliprant® <small>(grapiprant tablets)</small>	RIMADYL® <small>(carprofen)</small>	Previcox® <small>(firocoxib)</small>	Metacam® <small>(meloxicam)</small>
Proven effective for canine OA	●	●	●	●
Selectively blocks the EP4 receptor, the primary mediator of PGE ₂ -elicited peripheral sensitization (windup) and inflammation	●			
Does not disrupt production of prostaglandins important for organ health ^{1,2}	●			
Safety of the label dose supported by a laboratory study in healthy dogs receiving up to ~15x the dose daily for 9 months ³	●			
Stocked by more veterinary clinics in the U.S. than any other brand name NSAID ³	●			

Doesn't just mask pain; controls inflammation and pain at the source by targeting the EP4 receptor of PGE₂

Unique MOA reduces the impact on organ health^{4,5}

Proven effective at improving pain interference, pain severity, quality of life and veterinary assessments⁶

*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.

Visit galliprantvet.com, contact your Elanco sales representative or call Customer Service at (800) 633-3796.

REFERENCES

*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.

¹Attur M, Al-Mussawir HE, Patel J, et al. Prostaglandin E2 exerts catabolic effects in osteoarthritis cartilage: Evidence for signaling via the EP4 receptor. *J Immunol.* 2008;181:5082-8.

²Jang Y, Kim M, Hwang SW. Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. *J Neuroinflammation.* 2020;17(1):1-27.

³Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone.* 2012;51(2):249-57.

⁴Rausch-Derra LC, Huebner M, Rhodes L. Evaluation of the safety of long-term, daily oral administration of grapiprant, a novel drug for treatment of osteoarthritic pain and inflammation, in healthy dogs. *Am J Vet Res.* 2015;76(10):853-9.

⁵Kirkby 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.

⁶Rausch-Derra LC, Huebner M, Wofford J, Rhodes L. 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.* 2016;30:756-763.

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:

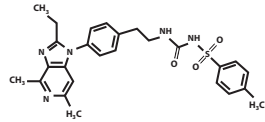
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

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 piprant 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.

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 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 antidiuretic 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

NADA 141-455, Approved by FDA

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.
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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.
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February 2018



Galliprant®

(grapiprant tablets)

For oral use in dogs only

Flavored tablets

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

Information for Dog Owners

GALLIPRANT is indicated for the control of pain and inflammation due to osteoarthritis.

This sheet contains important information about GALLIPRANT. You should read this information before starting your dog on GALLIPRANT and review it each time the prescription is refilled. This information provides a summary and does not take the place of the instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or you want more information about GALLIPRANT.

GALLIPRANT is a prostaglandin E₂ (PGE₂) EP4 receptor antagonist; a non-cyclooxygenase (COX) inhibiting, non-steroidal, anti-inflammatory drug (NSAID). As an anti-inflammatory, GALLIPRANT is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Control of pain and inflammation may vary from dog to dog. Consult your veterinarian if your dog appears to be uncomfortable. GALLIPRANT may need to be given for an extended period of time. Use the lowest dose to provide adequate pain control. Always consult with your veterinarian before altering the dose.

It is important to periodically discuss your dog's response to GALLIPRANT with your veterinarian. Your veterinarian will discuss appropriate monitoring while your dog is on GALLIPRANT.

The most common side effects associated with GALLIPRANT include vomiting, soft, mucoid stools, diarrhea and decreased appetite. You should contact your veterinarian if your dog's appetite decreases or stools become abnormal.

Dogs should not take GALLIPRANT if:

- Your dog is presently taking aspirin, other NSAIDs, or corticosteroids (unless directed by your veterinarian).
- Your dog has had an allergic reaction (such as hives, facial swelling, or itchy skin) to GALLIPRANT. Inform your veterinarian if your dog has had an allergic reaction to other anti-inflammatory drugs.
- Your dog is under 8 pounds in body weight.

GALLIPRANT should only be given to dogs. Do not use in cats.

GALLIPRANT should not be given with other non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (for example, aspirin, carprofen, meloxicam and prednisone).

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.

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

Tell your veterinarian about:

- Any side effects your dog has experienced from GALLIPRANT or other NSAIDs.
- Any digestive issues (bloody, mucoid stool, vomiting or diarrhea, or decreased appetite) your dog has.
- Any other medical problems or allergies that your dog has had.
- All medications that you are giving your dog or plan to give your dog, including those you can get without a prescription and any dietary supplements.
- If you plan to breed your dog, or if your dog is pregnant or nursing.

If you have additional questions about possible side effects while your dog is on GALLIPRANT, talk with your veterinarian or call 1-888-545-5973.

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February 2018

