

HOW CAN YOU TELL IF YOUR DOG HAS EARLY SIGNS OF OSTEOARTHRITIS?

Your dog can't tell you about aches and pains, so it's up to you to watch for the subtle warning signs of osteoarthritis pain and inflammation. No one knows your dog better than you do, so your veterinarian relies on you to notice changes in behavior.

ASK YOURSELF THESE QUESTIONS

- Y N 1. Is your dog less interested in participating in usual activities?
- Y N 2. Does your dog seem less alert?
- Y N 3. Does your dog lag behind during walks?
- Y N 4. Is your dog overly cautious when navigating stairs, jumping up on the couch, or getting in or out of the car?
- Y N 5. Is your dog sleeping more?
- Y N 6. Does your dog have difficulty getting up or lying down?
- Y N 7. Has your dog gained any weight?
- Y N 8. Does your dog seem less interested in greeting you when you come home?

If you answered yes to any of these questions, you should ask your veterinarian about possibly screening your dog for canine osteoarthritis.

YOUR VETERINARIAN MAY DECIDE TO MAKE GALLIPRANT® (grapiprant tablets) THE FOUNDATION OF YOUR DOG'S OSTEOARTHRITIS TREATMENT

Controlling the pain and inflammation associated with osteoarthritis is just part of what can help your dog stay active. Your veterinarian may also suggest other therapies to help manage your dog's condition.

TALK WITH YOUR VETERINARIAN TO DETERMINE THE BEST OVERALL PLAN TO HELP YOUR DOG FEEL BETTER

To learn more, please visit galliprantfordogs.com/brochure

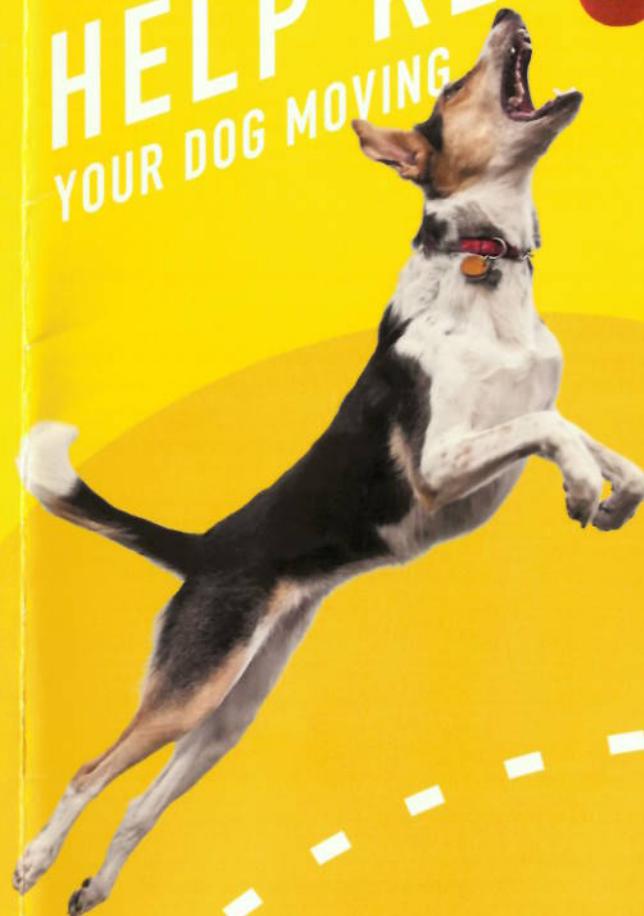
References

1. Fox, S. and Millis, D. 2010. "Osteoarthritis: The Disease." Multimodal Management of Canine Osteoarthritis: 24-29.
2. Kirkby Shaw, K., Rausch-Derra, L., and Rhodes, L. 2016. "Grapiprant: an EP4 prostaglandin receptor antagonist and novel therapy for pain and inflammation." Vet. Med. Sci. 2: 3-9.

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Galliprant
(grapiprant tablets)

HELP KEEP
YOUR DOG MOVING



LEARN THE BENEFITS
OF TREATING CANINE
OSTEOARTHRITIS

ARATANA

Elanco

NO NEED TO WAIT

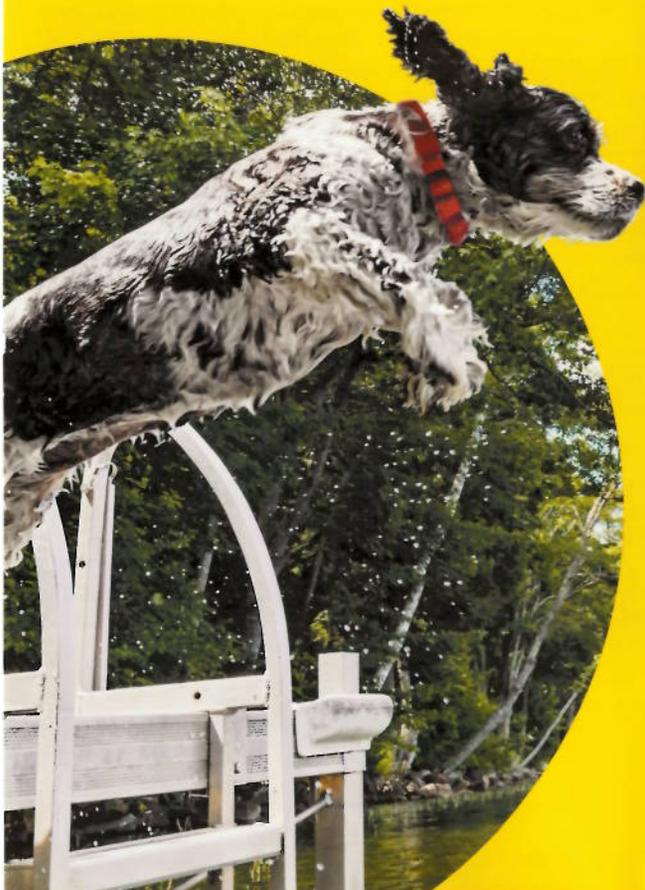
Small changes in your dog's behavior could actually be early signs of canine osteoarthritis. Your dog may be more cautious and slowing down because of achy joints.

WHAT IS CANINE OSTEOARTHRITIS?

Canine osteoarthritis is the most common cause of chronic pain in dogs,¹ and it doesn't just occur in older, heavy dogs. It's a painful disease that causes inflammation and swelling in a dog's joints.

A TREATABLE CONDITION

Although there's no cure for canine osteoarthritis, recognizing the possible signs early is important. Talk to your veterinarian today to learn more about canine osteoarthritis and how Galliprant® (grapiprant tablets) may help your canine friend stay active.



KEEP THEM DOING THE THINGS THEY LOVE

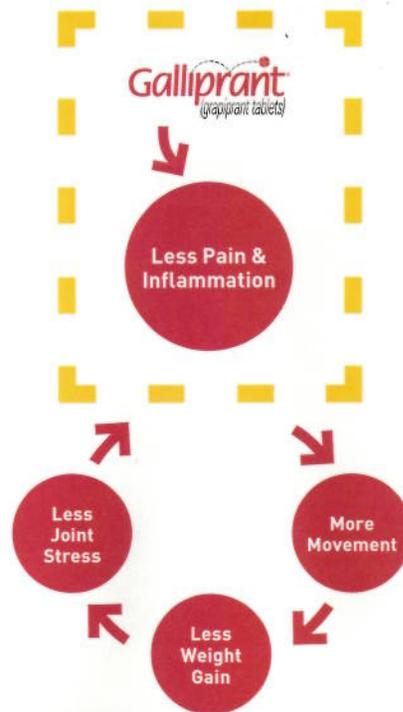
You want your dog to be able to run, jump and play. Galliprant reduces pain and inflammation, which can help dogs remain active. Your veterinarian may start treatment from the earliest diagnosed stages of osteoarthritis.

EARLY MANAGEMENT AND ITS BENEFITS

Once pain sets in, your dog is less likely to move and may put on a few extra pounds. That can put more stress on joints and may lead to even more inflammation and pain. It's a vicious cycle.

LESS INFLAMMATION AND LESS PAIN

Controlling osteoarthritis pain with Galliprant can help your dog maintain a normal activity level. With less pain and inflammation, your dog may be more eager to go on walks and play fetch again. And it might be easier for your canine friend to maintain a healthy weight, so joints don't become stressed.



HOW DOES GALLIPRANT WORK?

Galliprant directly blocks the key receptor involved in canine osteoarthritis pain and inflammation.²



GALLIPRANT

- Provides targeted control of your dog's pain and inflammation due to osteoarthritis
- Has been proven safe and effective
- Provides convenient, once-a-day dosing with whole or half tablets*

*Dosage should be calculated in half-tablet increments. Dogs weighing less than 8 lbs (3.6 kg) cannot be accurately dosed.

Galliprant is indicated for the control of 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. Please see product label on reverse side or call 1-888-545-5973 for full prescribing information.

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:

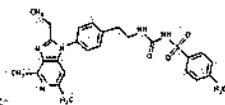
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

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 C₂₂H₂₂N₂O₅S. 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.

GALLIPRANT tablets are scored and 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
	150.1-220	68.1-100			2

To break the tablets in half, hold the tablet between the thumb and index finger of each hand on either side of the score line, with the score line facing downward. Separate into two halves by breaking the tablet down toward the score line.

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.

Continued monitoring is recommended.

stimulation of acid secretion in the stomach; inhibition of small intestine motility and inhibition of cytokine expression in the large intestine.¹ 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.²

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 (33100)
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	

¹ Study 1 was a food effect determination study.

² Study 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.

³ Median (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

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:

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 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,

the field study demonstrate that GALLIPRANT, administered at 2 mg/kg (0.9 mg/lb) 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

US Patent: 6,710,054

US Patent: 7,960,407

US Patent: 9,265,756

Made in New Zealand



Manufactured for:
Aratana Therapeutics, Inc.
Leawood, KS 66211

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.
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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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AT1-039-16

June 2016