Galliprant® (grapiprant tablets)

For canine osteoarthritis pain relief

GO WITH GALLIPRANT FROM THE START

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

Galliprant (grapiprant tablets)

Nearly **75%** of dogs

...are in the **MODERATE** or **SEVERE STAGES OF OA** before they begin treatment[1]

Untreated Early Canine Osteoarthritis

As a veterinarian, you want your patients to stay strong and active so they can do the things they love with their family, even with canine osteoarthritis (OA). But it can be challenging.

PAIN

Developmental disease or injury

Signs of OA may go unnoticed

Canine OA can start at a young age due to developmental joint disease or trauma, but initial clinical signs can be subtle and difficult for pet owners to see. This can lead to treatment delay.

SENSITIZATION

Pain cycle continues

OA pain

Uncontrolled pain has both adverse psychological and physiological consequences. Without pain control, the pain cycle continues with wind-up and ongoing sensitization.[2, 3, 4]

REDUCED ACTIVITY

Impact on daily life

More pain leads to less movement, loss of muscle mass and reduced strength—affecting everyday activities.

Chronic pain and advanced physical changes due to OA can be very difficult to manage.

EARLY detection of canine OA is a joint effort

Expand Your Canine OA Toolbox

Use these reliable resources as part of a multimodal rehabilitation plan to assess and monitor your patients' canine OA over time and to keep you in control of managing their OA pain and inflammation.

Engage pet owners

Educated pet owners can be on the lookout for OA behavioral changes early—helping you to see your OA patients sooner.

Earlier diagnosis

Early detection provides an opportunity to intervene and control OA pain earlier in its cycle.

Long-term OA care plan

A monitored, multimodal rehabilitation plan supports your patients' strength and mobility and keeps you in control of their OA pain.

Treat canine OA early so your patients can keep moving and doing the things they love.

Managing canine OA pain **EARLY**

Ask Your Elanco Representative For Details

COAST
Canine OsteoArthritis Staging Tool
Staging & Monitoring[3]

LOAD
Pet Owner Questionnaire

EnCORE
Canine Exam

As First-Line Treatment

Galliprant® (grapiprant tablets) WORKS DIFFERENTLY

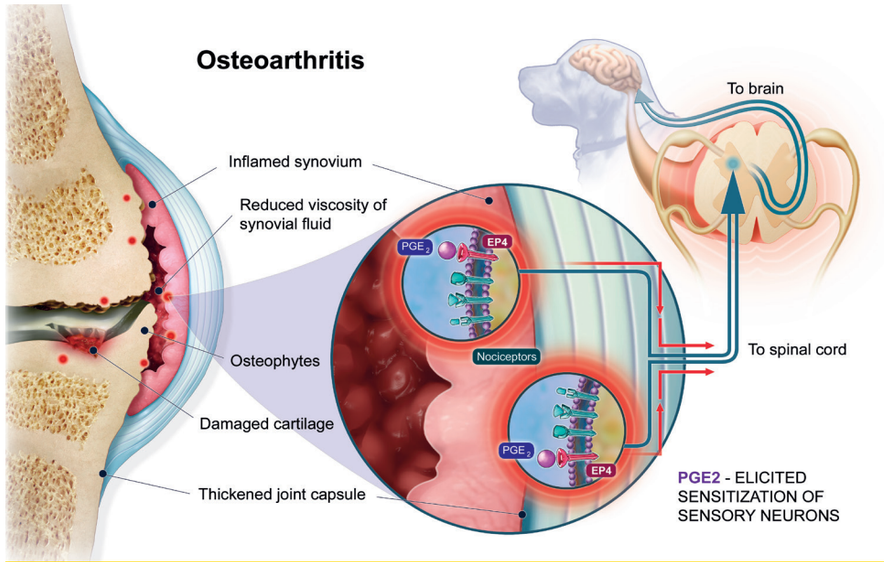
It's a non-COX inhibiting NSAID › that specifically blocks the PGE_2 EP4 receptor[5] › to control pain and inflammation in dogs with OA

Canine OA

Canine OA is characterized by intermittent inflammation and degradation of cartilage, leading to chronic, progressive pain and mobility challenges.

Mediating OA Pain and Inflammation[5]

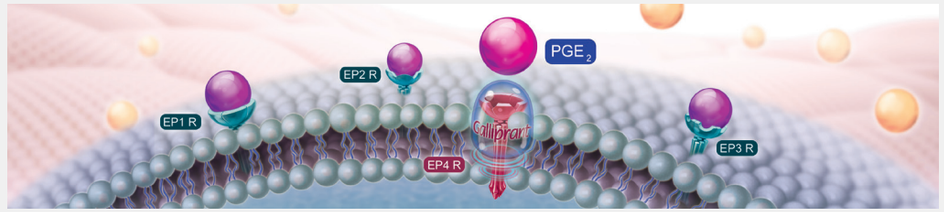
The EP4 receptor is the primary mediator of PGE_2-elicited sensitization of sensory neurons and PGE_2-elicited inflammation. Activation of the EP4 receptor by PGE_2 leads to sensitization of sensory neurons and inflammation.



Rethink Canine OA Pain Relief

A Mode of Action Unlike Any Other

Galliprant controls PGE_2-elicited pain and inflammation by selectively antagonizing the EP4 receptor, reducing the severity of pain and its interference with daily activities.



Improvement in Pain and Function

In evaluating the effectiveness of Galliprant for dogs with OA pain, pet owners provided feedback using the Canine Brief Pain Inventory (CBPI). The CBPI enabled owners to rate the severity of their dog's pain and how much the pain interfered with daily function and activities.

The CBPI is one of the most extensively validated pet owner questionnaires.


Pain severity


General activity


Enjoyment of life


Ability to climb the stairs


Ability to rise


Ability to walk


Ability to run

Galliprant can help you provide daily relief for canine OA pain.

More detailed information about the pivotal study is provided on the next page.

SELECT 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.

PROVEN OA PAIN RELIEF WITH Galliprant® (grapiprant tablets)

STUDY

Evaluations Performed by Pet Owners and Veterinarians

262 client-owned dogs treated per protocol for naturally occurring OA.

Two groups (131 dogs per group) with radiographic and clinical signs of mild, moderate or severe OA

- ☑ PROSPECTIVE
- ☑ RANDOMIZED
- ☑ BLINDED

Galliprant

2 mg/kg p.o. once daily for 28 days

Treated dogs:
- 2 to 16.75 yrs old
- 9 to 131 lbs

Placebo

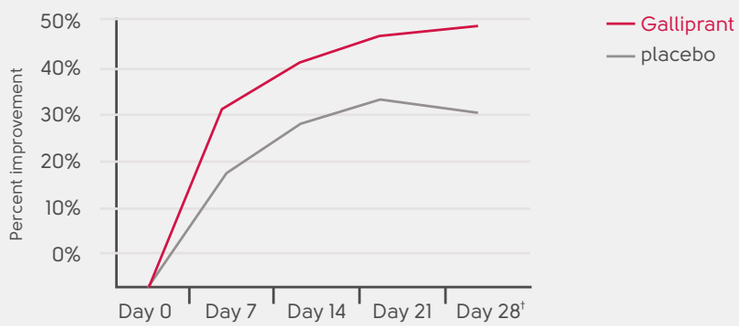
Once daily for 28 days

Evaluations by Pet Owners

Greater Treatment Success With Galliprant

Dogs assessed for improvement in pain and function using the Canine Brief Pain Inventory (CBPI).

Treatment Success[6]



Per protocol population, statistically significant ($P<0.05$) differences between groups at all measured time points (comparison to Day 0).

†Primary effectiveness variable = CBPI score on D28 compared to D0 (treatment success failure criteria).

Greater treatment success vs placebo seen during the first week of treatment and improvements continued throughout the study period.

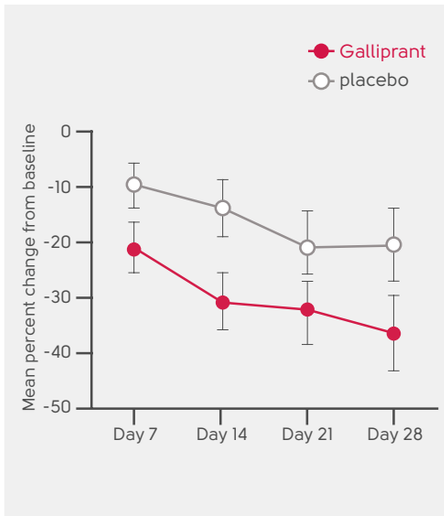
Dogs had to have a CBPI pain severity score ≥2 and a pain interference score ≥2 for enrollment. Treatment success using the CBPI is defined as improvement in pain severity score of 2 or more AND improvement in pain interference score of 1 or more AND overall assessment had to be the same or better.

Significant Improvements in Owner-Assessed Pain and Function

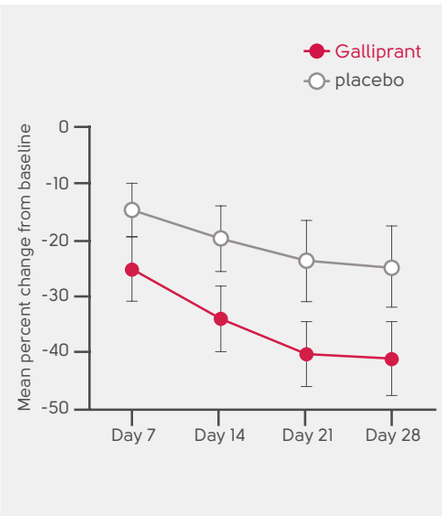
Statistically significant†† greater improvement (reduction in **pain severity AND pain interference**) on days **7, 14, 21 and 28 with Galliprant.**

- ✓ Day 7
- ✓ Day 14
- ✓ Day 21
- ✓ Day 28

Pain Severity Score[6]



Pain Interference Score[6]



Comparison of CBPI scores (mean percentage change from Day 0) between groups. ††$P<0.05$ at all timepoints.

SELECT IMPORTANT SAFETY INFORMATION

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

PROVEN OA PAIN RELIEF WITH Galliprant® (grapiprant tablets)

Evaluations by Veterinarians

Recommend With Confidence

Dogs assessed in-clinic for effectiveness using the Total Orthopedic Score (TOS).

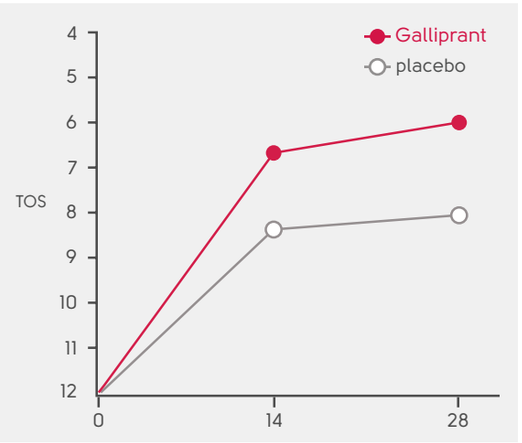
Total Orthopedic Score = Sum of Scores for 7 Components

Each component score range: 0=unremarkable to 4=severely affected			
			Pain/resistance on palpation
	Weight bearing		Abnormality in extension (RoM)
	Limb raise (contralateral)		Swelling
	Lameness (walk)		Lameness (trot)

Significant Improvements in Veterinarian-Assessed Pain and Function

Greater improvement in Total Orthopedic Scores (TOS) with Galliprant compared to placebo (statically significant¶), both on day 14 and day 28 (D14: *P*=0.0029; D28: *P*=0.0086).[6]

Total Orthopedic Scores



Comparison of mean TOS scores between groups.
¶*P*<0.01 at both timepoints; a lower TOS is better.

EFFECTIVE
treatment and control of pain and inflammation associated with OA in dogs.

SELECT IMPORTANT SAFETY INFORMATION
Do not use in dogs that have a hypersensitivity to grapiprant.

Galliprant® (grapiprant tablets)

USE AS FIRST-LINE TREATMENT

Treat canine OA pain and inflammation EARLY ON and use for as long as needed*‡

Galliprant is an NSAID that works differently to control pain and inflammation associated with osteoarthritis in dogs.

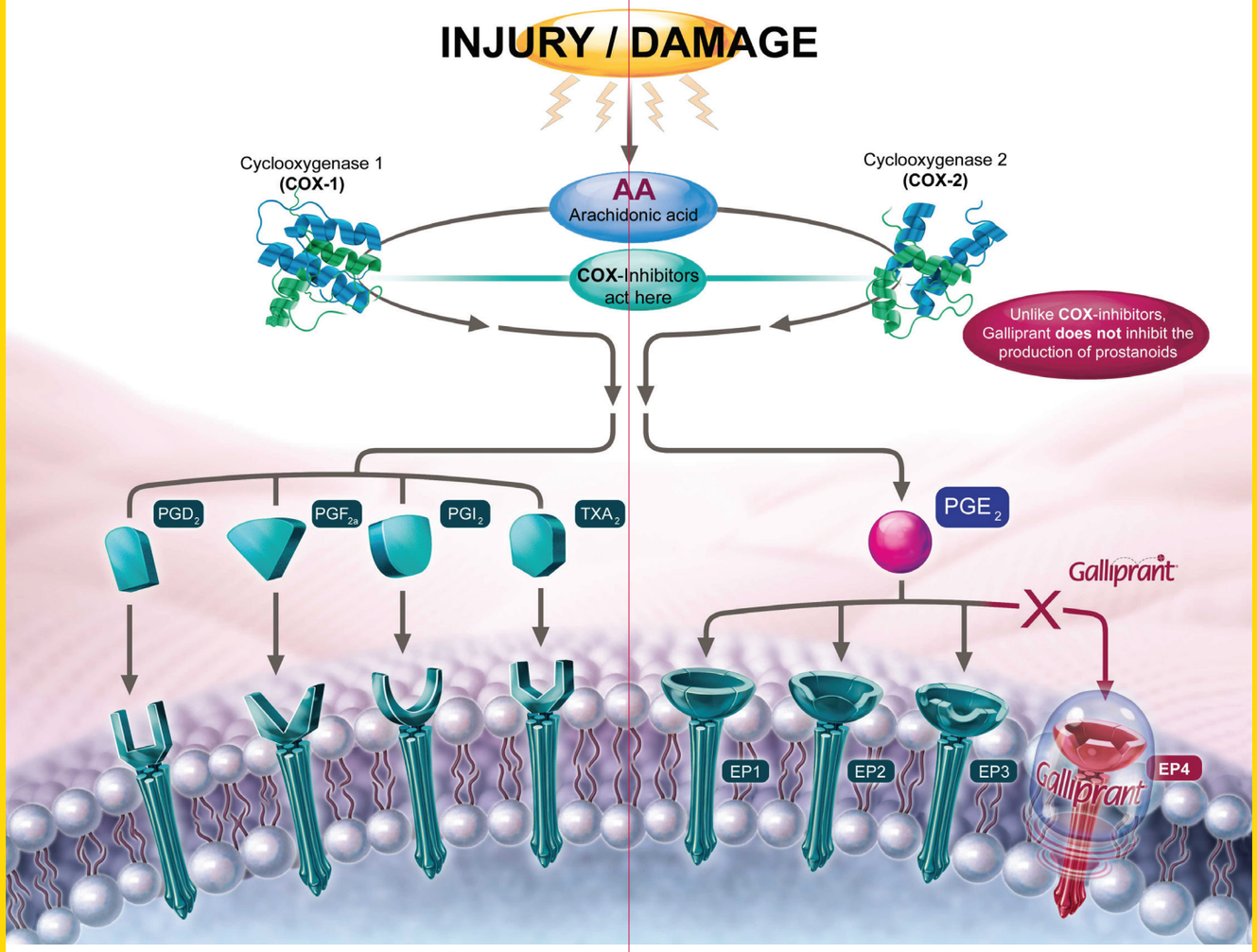
FOR ALL STAGES of OA, from the earliest clinical signs.*

SAFE to use daily.

" I feel comfortable choosing Galliprant as a first-line option for my OA cases. "

Kristin Kirkby Shaw,
DVM, MS, PhD, DACVS, CCRT, DACVASMR

*Approved for use in dogs older than 9 months of age and greater than 8 pounds.
‡Monitoring is recommended if used long term.



Reduces impact on homeostatic "house-keeping" functions mediated through other receptors.

Blocks the primary mediator of OA pain and inflammation.

Galliprant is a **FIRST-IN-CLASS** non-COX inhibiting NSAID.

It specifically **TARGETS** the prostaglandin E_2 EP4 receptor.

Its mode of action **TARGETS** canine OA pain and inflammation, while reducing the impact on GI, kidney and liver homeostasis.[5,7‡]

SELECT IMPORTANT SAFETY INFORMATION

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.

SELECT IMPORTANT SAFETY INFORMATION

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.

Galliprant®
(grapiprant tablets)

TREAT WITH GALLIPRANT FROM THE EARLIEST DIAGNOSED STAGES OF CANINE OA AND FOR AS LONG AS NEEDED*‡

Pill images are not actual size

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

Dogs weighing less than 8 lbs (3.6 kg) cannot be accurately dosed. Only the 20 mg and 60 mg tablets of Galliprant are scored. Dosages should be calculated in half-tablet increments, except when using the 100 mg tablet because it is not scored and should not be broken in half. For dogs weighing more than 150 lbs (68 kg), use a combination of tablets and half tablets to achieve the appropriate dose.

*Approved for use in dogs older than 9 months of age and greater than 8 pounds.
‡Monitoring is recommended if used long-term.

SELECT IMPORTANT SAFETY INFORMATION

The most common adverse reactions were vomiting, diarrhea, decreased appetite, and lethargy. For complete safety information see product label.

CONTACT YOUR ELANCO REPRESENTATIVE TO INCORPORATE GALLIPRANT INTO YOUR OA PAIN PROTOCOL TODAY

1. Elanco. Data on file.
2. Lascelles D. International Association for the Study of Pain, 2016, Fact Sheet No. 9.
3. Cachon T, el al. Vet J. 2018 May 1;235:1-8.
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5. Kirkby Shaw K, et al. Vet Med Sci. 2016;2:3-9.
6. Rausch-Derra L, et al. J Vet Intern Med. 2016;30:756-763.
7. Rausch-Derra L, et al. Am J Vet Res. 2015;769(10):853-859.

For more information, please visit **GalliprantVet.com**

Galliprant®
(grapiprant tablets)

For oral use in dogs only

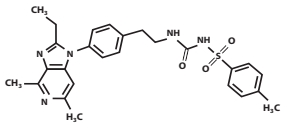
20 mg, 60 mg and 100 mg flavored tablets

A prostaglandin E_2 (PGE_2) 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 E_2 (PGE_2) 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 $C_{26}H_{29}N_5O_3S$. 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 E_2 (PGE_2) EP4 receptor antagonist; a non- cyclooxygenase inhibiting, non-steroidal, anti-inflammatory drug. Grapiprant has a canine EP4 receptor binding affinity (Ki) of 24 nM.

Prostaglandins have a wide variety of physiologic effects. Prostaglandin E_2 (PGE_2) is a prostanoid that exerts its effects via four receptors, EP1, EP2, EP3, and EP4. PGE_2 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 PGE_2-elicited sensitization of sensory neurons[1] and PGE_2-elicited inflammation.[2] Grapiprant blocks PGE_2-elicited pain and inflammation by antagonizing the EP4 receptor.

The EP4 receptor, along with the EP1, EP2 and EP3 receptors, is involved in PGE_2 mediated effects on gastrointestinal homeostasis and renal function. PGE_2 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 PGE_2 gastroprotective action is mediated by EP1, the healing-promoting action of PGE_2 in the stomach is mediated by the EP4 receptor.[4] In the kidney, the PGE_2 antinatiuretic 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	

[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 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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February 2018