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 C₂₃H₂₄N₂O₂S. Grapiprant is N-(2-[4-(2-Ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]-ethylaminocarbonyl)-4-methylenesulfonamido.
The structural formula is:

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\begin{array}{c}
\text{N} \\
\text{O} \\
\text{S} \\
\end{array}
\]
\]

Indication:
GALLIPRANT (grapiprant tablets) is indicated for the control of pain and inflammation associated with osteoarthritides 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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Weight in lbs</th>
<th>Weight in kilograms</th>
<th>20 mg tablet</th>
<th>60 mg tablet</th>
<th>100 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9 mg/lb</td>
<td>8-15</td>
<td>3.6-6.8</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>15.1-30</td>
<td>6.9-13.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-45</td>
<td>13.7-20.4</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45.1-75</td>
<td>20.6-34</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75.1-150</td>
<td>34.1-68</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 kgs), 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, anticoagulant 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.

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

*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 (Kᵢ) of 24 nM.
Prostaglandins have a wide variety of physiologic effects. Prostaglandin E₂ (PGE₂) is a prostanoïd 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 mucous 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, anti-inflammatory 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 proxiexa.
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 (hydroxy) 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Parameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(0.5 – 1.03)</td>
<td>(0.5 – 0.87)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(1.0 – 2.0)</td>
<td>(1.0 – 4.0)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1210</td>
<td>1210</td>
</tr>
<tr>
<td></td>
<td>(341)</td>
<td>(319)</td>
</tr>
<tr>
<td>AUC(0-inf) (ng hr/mL)</td>
<td>2790</td>
<td>2790</td>
</tr>
<tr>
<td></td>
<td>(982)</td>
<td>(961)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>4.60</td>
<td>4.60</td>
</tr>
<tr>
<td></td>
<td>(4.19)</td>
<td>(3.27)</td>
</tr>
</tbody>
</table>

Medications:

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)
Galliprant is a prostaglandin E2 (PGE2) EP4 receptor antagonist; a non-cyclooxygenase 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.

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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 (for example, aspirin, carprofen, meloxicam and prednisone).
- 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.
- Any 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 1-888-545-9973.

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For oral use in dogs only

**Flavored tablets**


**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.