GALLIPRANT® (grapiprant tablets)

For oral use in dogs only

20 mg, 60 mg and 100 mg flavored tablets

A prostaglandin E₃ (PGE₃) 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 E₃ (PGE₃) 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 C₂₆H₂₃N₂O₂S. Grapiprant is N-[2-[4-(2-Ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl]amine|carbonyl|-4 methylbenzenesulfonamide. The structural formula is:

![Structural formula of Grapiprant]

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 kg) cannot be accurately dosed.

Dosing Chart

<table>
<thead>
<tr>
<th>Dose</th>
<th>Weight in pounds</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>8-15</td>
<td>3.6-6.8</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.1-30</td>
<td>6.9-13.6</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30.1-45</td>
<td>13.7-20.4</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45.1-75</td>
<td>20.5-34</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75.1-150</td>
<td>34.1-68</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150.1-220</td>
<td>68.1-100</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. 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>
<thead>
<tr>
<th>Table 1. Adverse reactions reported in the field study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Diarrhea, soft stool</td>
</tr>
<tr>
<td>Anorexia, inappetence</td>
</tr>
<tr>
<td>Lethargy</td>
</tr>
<tr>
<td>Buccal ulcer</td>
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<tr>
<td>Immune mediated hemolytic anemia</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 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 E₃ (PGE₃) 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 E₃ (PGE₃) is a prostaglandin that exerts its effects via four receptors, EP1, EP2, EP3, and EP4. PGE₃ 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 PGE₃-elicited sensitization of sensory neurons² and PGE₃-elicited inflammation.³ Grapiprant blocks PGE₃-elicited pain and inflammation by antagonizing the EP4 receptor.

The EP4 receptor, along with the EP1, EP2 and EP3 receptors, is involved in PGE₃-mediated effects on gastrointestinal homeostasis and renal function. PGE₃ 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 PGE₃, gastroprotective action is mediated by EP1, the healing-promoting action of PGE₃ in the stomach is mediated by the EP4 receptor.

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

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.

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.
significant differences in owner assessed pain and function. The results group (41/131 or 31.3%). GALLIPRANT demonstrated statistically difference in the proportion of treatment successes in the GALLIPRANT assessed for improvements in pain and function by the owners using the 285 dogs were included in the effectiveness evaluation. Dogs were NSAID or other current OA therapy. Two hundred and sixty two (262) of placebo-controlled, masked field study. Dogs had a 7-day washout from with radiographic and clinical signs of osteoarthritis were enrolled in a study and evaluated for field safety. GALLIPRANT-treated dogs ranging in grapiprant was ~95%. (major metabolite urine (3.4%) and feces (7.2%)) and one N-oxidation were identified; two hydroxylated metabolites, one N-deamination metabolite 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, 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 kg (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. 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 hypoprotenemia 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: 9,265,756
Made in New Zealand

**References:**


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