**GALLIPRANT®** (grapiprant tablets)

For oral use in dogs only

20 mg, 60 mg and 100 mg flavored tablets

A prostaglandin E	extsubscript{2} (PGE	extsubscript{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	extsubscript{2} (PGE	extsubscript{2}) EP4 receptor antagonist; a non-cyclooxygenase (COX) inhibiting, non-steroidal anti-inflammatory drug (NSAID) in the piroctone 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 \( C_{26}H_{33}N_{5}O_8S \). 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:

\[
\text{CH}_3
\]
\[\text{N}\]
\[\text{H}_2\text{C} \]
\[\text{C} \]
\[\text{H}_3\text{C} \]
\[\text{N} \]
\[\text{NH}_2\text{O} \]
\[\text{S} \]
\[\text{O} \]

**Indication:**

GALLIPRANT (grapiprant tablets) is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

**Dosage and Administration:**

**Caution:**

Veterinarians should instruct pet owners on the management of their pet if pain or inflammation is not adequately controlled by the use of GALLIPRANT. GALLIPRANT use may result in a decrease in appetite and should be continued only if the pet is eating well and maintaining normal body weight.

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**

<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>0.9 mg/lb (2 mg/kg) once daily</td>
<td>8-15</td>
<td>3.6-6.8</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.1-30</td>
<td>6.9-13.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.1-45</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>20.5-34</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>
<tr>
<td></td>
<td>150.1-220</td>
<td>68.1-100</td>
<td>2</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 downward 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 veterinarian 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, wet or bloody stools, and decreases in serum albumin and total protein.

**Warnings:**

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/AnimalVets/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	extsubscript{2} (PGE	extsubscript{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	extsubscript{2} (PGE	extsubscript{2}) is a prostanoid that exerts its effects via four receptors, EP1, EP2, EP3, and EP4. PGE	extsubscript{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	extsubscript{2}-elicted sensitization of sensory neurons and PGE	extsubscript{2}-elicited inflammation. Grapiprant blocks PGE	extsubscript{2}-elicited pain and inflammation by antagonizing the EP4 receptor.

(continued on other side)
The EP4 receptor, along with the EP1, EP2 and EP3 receptors, is involved in PGE-mediated effects on gastrointestinal homeostasis and renal function. PGE effects are mediated solely by the EP4 receptor, and are modulation 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. While PGE, gastroprotective action is mediated by EP1, the healing-promoting action of PGE in the stomach is mediated by the EP4 receptor. In the kidney, the EP4 anti-natriuretic effect is mediated by the EP4 receptor. 

EP4 receptors are abundantly expressed in the heart of dogs, the clinical relevance of which is unknown. The EP4 receptor is not involved in generation of pyrexia. 

Grapiprant is a non-potential inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP3A4 and CYP3A44 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 2</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>2 mg/kg (n = 10) (Fasted)</td>
<td>2 mg/kg (n = 10) (Fed)</td>
<td>6 mg/kg (n = 8) (Fasted)</td>
<td>50 mg/kg (n = 8) (Fasted)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.0 (0.5 – 1.03)</td>
<td>1.0 (0.5 – 0.8)</td>
<td>1.0 (1.0 – 2.0)</td>
<td>2.0 (1.0 – 4.0)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1210 (341)</td>
<td>278 (179)</td>
<td>5720 (3220)</td>
<td>9850 (13100)</td>
</tr>
<tr>
<td>AUC(0-inf) (ng·hr/mL)</td>
<td>2790 (982)</td>
<td>1200 (523)</td>
<td>17800 (5520)</td>
<td>414000 (73700)</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>4.60 (4.19)</td>
<td>5.67 (3.27)</td>
<td>5.01 (1.95)</td>
<td>5.21 (1.66)</td>
</tr>
<tr>
<td>Fed/Fasted Relative Bioavailability</td>
<td>0.37 (0.28 – 0.46)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 × 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. 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. A statistically significant difference in the proportion of treatment successes in the GALLIPRANT group (63/131 or 49.1%) 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

US Patent: 6,710,054


US Patent: 9,265,756

Made in New Zealand

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