



Zonisamide

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The popularity and use of zonisamide in veterinary patients has rapidly increased in recent years.

CLINICAL APPLICATIONS

Zonisamide is used as an anticonvulsant in dogs and cats.

- ▶ Based on the author's clinical experience, zonisamide may be effective when used as monotherapy or in conjunction with other anticonvulsants (eg, phenobarbital, potassium bromide, levetiracetam).
- ▶ In some cases, zonisamide may reduce seizure frequency by up to 70% to 80%.^{1,2}
- ▶ Zonisamide is available in generic form, which makes it more affordable than when first introduced.

MECHANISM OF ACTION & PHARMACOKINETICS

Zonisamide's exact mechanism of action is not completely understood.

- ▶ It is known to block sodium channels, suppress inward

calcium currents, enhance neuronal inhibition, and weakly inhibit carbonic anhydrase.³

Zonisamide is metabolized by hepatic microsomal enzymes.

- ▶ In dogs, the half-life is ≈15 hours, with steady state reached in 3 to 4 days.^{4,5}
- ▶ In cats, the half-life is ≈33 hours, with steady state expected in ≈1 week.⁶

PROTOCOL

In dogs, a starting dosage of 3-5 mg/kg PO q12h is recommended.^{4,7}

- ▶ Concurrent use of phenobarbital may speed up zonisamide clearance, necessitating monitoring and dose adjustments.⁵
 - When used in combination with phenobarbital, the recommended starting dose for zonisamide is 10 mg/kg PO q12h.

In cats, a starting dose of 5-10 mg/kg PO q24h is recommended, although further research is necessary.⁸

Rectal dosing of zonisamide for the control of status epilepticus is not recommended.⁹

- ▶ An IV form is not commercially available.

The author recommends therapeutic monitoring on a case-by-case basis to track trends, but it may not be necessary in all cases.

- ▶ Serum or plasma zonisamide levels should be monitored no earlier than 1 week after initiation of therapy or a dose change.⁴
 - A serum level of 10-40 µg/mL is targeted based on therapeutic concentrations established in human medicine.
 - More research is needed to establish a therapeutic range for dogs and cats.

ADVERSE EVENTS & CAUTIONS

Zonisamide is considered to have a wide margin of safety.

- ▶ In dogs, typically only mild side effects (eg, sedation, lethargy, ataxia, vomiting) are seen.¹
- ▶ 50% of cats receiving 20 mg/kg PO q24h for 9 weeks suffered adverse events, including anorexia, diarrhea, vomiting, somnolence, and ataxia.⁶

Published case reports have documented serious and potentially fatal adverse events, including drug-induced acute liver failure, renal tubular acidosis, and, most recently, erythema multiforme in individual dogs.¹⁰⁻¹³

Zonisamide may affect thyroid hormone synthesis and circulating levels of thyroid hormone.

- ▶ It is important to establish baseline thyroid function before beginning zonisamide therapy.⁴
- ▶ In patients receiving zonisamide therapy, the author recommends checking zonisamide levels, CBC, and serum chemistry profile 2 weeks and 3 months after beginning initial therapy and every 6 to 12 months thereafter, depending on patient's seizure control and clinical status. ■■■

Serum or plasma zonisamide levels should be monitored no earlier than 1 week after initiation of therapy or a dose change.⁴

Continues on page 118

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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.

Before using this product, please consult the product insert, a summary of which follows:

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. **See product insert for complete dosing and administration information.**

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:

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.

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 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.

Storage Conditions: Store at or below 86° F (30° C)

How Supplied: 20 mg, 60 mg, 100 mg flavored tablets in 7, 30 and 90 count bottles.

NADA 141-455, Approved by FDA

US Patents: 6,710,054; 7,960,407; 9,265,756

Made in New Zealand Manufactured for: Aratana Therapeutics, Inc., Leawood, KS 66211

Reference: 1. http://www.vet.upenn.edu/docs/default-source/VVIC/canine-bpi_userguide.pdf?sfvrsn=0

Additional information is available at 1-888-545-5973.

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