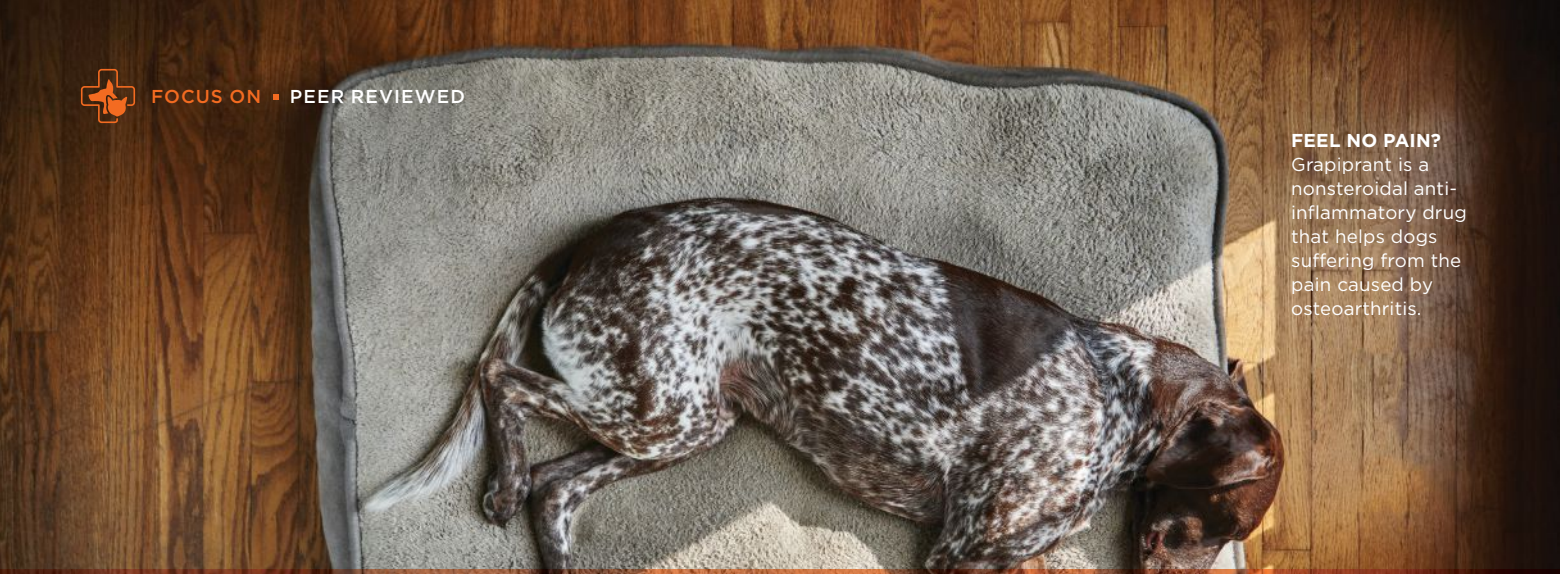

FEEL NO PAIN? Grapiprant is a nonsteroidal anti-inflammatory drug that helps dogs suffering from the pain caused by osteoarthritis.

FOCUS ON

Grapiprant for Control of Osteoarthritis Pain in Dogs

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For centuries, nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for pain control. However, their use has been associated with potentially life-threatening adverse drug events. Grapiprant is a novel drug for treatment of osteoarthritic pain in dogs. Approved in 2016, it is a non-cyclooxygenase (COX)-inhibiting NSAID. Grapiprant is a highly selective, potent inhibitor of the prostaglandin (PG) E_2 EP_4 receptor, which is primarily responsible for the pain and inflammation associated with osteoarthritis.[1] Grapiprant works downstream of traditional NSAIDs in the arachidonic acid cascade. A review of the arachidonic acid cascade and its role in inflammation can be found in a recent review.[2]

In the United States, grapiprant has been approved for treatment of osteoarthritis in dogs. However, because it has only been 3 years since drug approval, nonbiased controlled clinical trials have not yet compared its safety or efficacy with that of other NSAIDs. Although grapiprant has not been on the market long enough for clinical trials and adverse events to be effectively assessed, this report reviews the existing literature about its safety or efficacy, especially information about its use in dogs with osteoarthritis. Grapiprant is not approved for use in cats.

PHARMACODYNAMICS

Grapiprant belongs to the piprant class of drugs, which are prostaglandin receptor antagonists; grapiprant selectively targets EP_4.[1,3] However, despite this selectivity, because of the diverse locations of EP_4 receptors and physiological responses to prostaglandin mediated by EP_4, grapiprant has the potential to influence multiple actions of PGE_2. For example, PGE_2/EP_4 homeostatic interactions include gastrointestinal, hemostatic, renal, and immune regulation.[4] Other functions include wound healing, bone metabolism, and skin immunity.[5,6] Although its primary ligand is PGE_2, EP_4 also binds to $PGF_{2\alpha}$ and PGE_1, but it is not clear whether physiologic responses to these ligands are blocked by grapiprant.[7]

Because grapiprant's antagonism of the EP_4 receptor seems to be selective, its effects at other sites are minimized.[1,3,8] The magnitude of effect increases with plasma concentration. Binding is competitive, suggesting that efficacy is time-dependent, further suggesting that the dosing interval be based on elimination.[5] According to in vitro studies of receptors in dogs and rodent and human pain models, the minimum plasma drug concentration for efficacious analgesia in dogs is 114 to 164 ng/mL.[8] The dose needed to achieve this concentration, based on pharmacokinetic studies in dogs, is 2 mg/kg.[8] However,

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according to Freedom of Information laws in Europe, the dose justification has not been fully supported and more than one dose a day may be necessary.[9]

PHARMACOKINETICS

Several studies have described the disposition of grapiprant in dogs.[8,10,11] Key pharmacokinetic parameters covered here are oral bioavailability, tissue distribution, and elimination.

Oral Bioavailability

Oral disposition presents some factors that influence bioavailability. In female Labrador retrievers, grapiprant given as a pure powder in a capsule was approximately 100% orally bioavailable when given to fasted animals, but only 60% bioavailable when given to fed animals.[10] Furthermore, the time to peak plasma concentration was prolonged from 1 (fasted) to 3 hours, and the peak plasma concentration was reduced by approximately 40% when animals were fed. Study findings that plasma concentrations remained above the presumed minimum effective concentration (164 ng/mL) for approximately 6 hours regardless of feeding suggest that the drug can be given with food[10]; however, efficacy might be affected and clients should be consistent as to how they administer the drug. Oral bioavailability is also affected by formulation, being 40% to 60% higher when given as the approved tablet rather than as a suspension.[11] As such, manipulation of the approved formulation, including use of compounded grapiprant, should be avoided. If the tablet is scored (e.g., 20 and 60 mg), the dose can be calculated in half-tablet increments. If not scored (e.g., 100 mg), equal distribution of drug cannot be assumed and equal dosing may not occur with each drug half. No evidence could be found to address efficacy of crushed tablets.

In fasted beagles, oral bioavailability increased disproportionately more than dose, suggesting saturation of drug-metabolizing enzymes or transporters.[8] Another study demonstrated an increase of 20- to 25-fold in maximum serum concentration and area under the curve in 4 beagles receiving 6 or 50 mg/kg.[11] As such, care should be taken to avoid overdosing, and extra caution may be indicated for patients when hepatic function is of concern.

Tissue Distribution

As with other NSAIDs, grapiprant is highly (about 95%) bound to plasma proteins,[5] and its displacement can increase unbound, pharmacologically active drug. However, clearance is likely to increase for the unbound drug. Nonetheless, caution may be indicated when using grapiprant with other highly protein-bound drugs (e.g., cefovecin, doxycycline), particularly if hepatic function is impaired. High binding to proteins at the site of inflammation may prolong efficacy beyond that predicted by its half-life.

An elimination half-life of approximately 5 hours indicates that the drug will not significantly accumulate in healthy dogs after 24-hour dosing.[11]

Elimination

Grapiprant is cleared primarily via cytochrome-mediated (CYP450) hepatic metabolism, although the specific enzymes have not been identified. Differences in CYP450 metabolism are increasingly being identified as a possible cause of adverse drug events among dogs of different breeds.[12] Furthermore, for other NSAIDs, polymorphisms resulting in different rates of hepatic metabolism (poor to ultra-efficient metabolizers) have been identified in dogs.[13] Grapiprant metabolites are excreted in bile, urine, and feces, but neither the extent of metabolism nor enterohepatic circulation have been reported. An elimination half-life of approximately 5 hours indicates that the drug will not significantly accumulate in healthy dogs after 24-hour dosing.[11] After grapiprant administration is discontinued, most of the drug will be eliminated within 24 hours. Indeed, during a 24-hour dosing interval, approximately 90% of the drug will be eliminated within 15 hours, leaving a substantive drug-free period for organs of elimination, which may facilitate safety. Efficacy may be affected, although binding of NSAIDs to inflammatory proteins at the site of action has been demonstrated to contribute to a longer than expected duration of effect, based on elimination half-life.[14,15]

Safety of grapiprant in dogs that weigh less than 3.6 kg or are younger than 9 months has not been established.

As with all NSAIDs, the lowest minimum effective dose should be established for each patient. A duration of administration has not been stipulated.

EFFICACY

Evidence of grapiprant's efficacy is largely limited to field trials implemented during the approval process. All clinical trials were based on a placebo rather than a positive control (NSAID). In 1 trial, 262 dogs (131 per treatment group) with osteoarthritis, ranging from 2 to 17 years of age and weighing 4 to 60 kg, received either placebo or grapiprant at the labeled dose of 2 mg/kg PO q24h for 28 days.[16] Evidence of efficacy was based on client-completed Canine Brief Pain Inventory responses and was considered successful for 48% of dogs receiving grapiprant and only 31% receiving placebo. However, the implication of this narrow efficacy difference (17%) warrants further consideration. According to the U.S. Food and Drug Administration (FDA) adverse event reporting site (fda.gov/animal-veterinary/safety-health), the fourth most common adverse event recorded for grapiprant was lack of efficacy, yet this effect was noted in only 1.4% of dogs receiving the comparison drug, deracoxib (TABLE 1). These data indicate a need for head-to-head randomized controlled clinical trials comparing grapiprant efficacy with that of other NSAIDs.

SAFETY/ADVERSE EVENTS

The potential safety of grapiprant is supported by 3 sources: animal safety studies, field trials implemented during the approval process (as reported in the Freedom of Information Act and the product package insert), and postmarket surveillance.

Animal Safety Studies

Among 8 beagles receiving 1 or 50 mg/kg

TABLE 1 Adverse Drug Events for Dogs Receiving Grapiprant and Deracoxib, Reported to the Food and Drug Administration Center for Veterinary Medicine Reporting Site*

ADVERSE EVENT	GRAPIPRANT NO. (%)	DERACOXIB NO. (%)
Total†	**2,272**	**10,070**
Diarrhea‡	703 (30.94)	1,378 (13.7)
Vomiting/emesis	516 (22.71)	3,384 (33.6)
Anorexia§	450 (19.81)	2,330 (23.1)
Ineffective as an anti-inflammatory¶	402 (17.69)	140 (1.4)
Lethargy	291 (12.81)	413 (4.1)
Euthanasia	134 (5.90)	1,146 (11.4)
Elevated ALT	130 (5.72)	1,241 (12.3)
Increased creatinine	119 (5.24)	1,330 (13.2)
Weight loss	112 (4.93)	573 (5.7)
Elevated SAP#	106 (4.67)	1,556 (15.5)
Increased BUN	99 (4.36)	1,567 (15.6)
Death	43 (1.89)	995 (9.9)
Melena/blood in vomitus	39 (1.72)	848 (8.4)
Renal failure	16 (0.70)	152 (1.5)
Intestinal perforation	0	542 (12.7)
Peritonitis	0	575 (5.7)
GI ulceration**	0	372 (3.7)

**Reporting site is fda.gov/animal-veterinary/safety-health.*
ALT=alanine aminotransferase; BUN=blood urea nitrogen; GI=gastrointestinal; SAP=serum amyloid protein.
†Data not corrected for number of units sold.
‡Including bloody diarrhea (n = 160) and loose stools (n = 95).
§Also reported as decreased appetite, not eating, or, inappetance.
¶Including lack of anti-inflammatory efficacy (122).
#Including increased ALT (n = 130) as well as SAP (n = 106).
***Gastric and intestinal.*

grapiprant PO q24h for 9 months (4 dogs/group), no serious clinical-pathologic adverse drug events were noted. Although total serum protein and albumin concentrations decreased significantly compared with those of controls, all remained within normal limits.[17] Indicators of hemostasis did not change. A second study, also among beagles, demonstrated that grapiprant at 6 or 50 mg/kg/day for 15 days was well tolerated.[11] In contrast, studies of deracoxib cited in the product package insert revealed abnormalities consistent with altered renal function in dogs receiving 5 times the recommended dose for 6 months, as well as vomiting, melena, and gastrointestinal lesions in dogs receiving 5 to 50 times the recommended dose for 14 days.

Field Trials

Data from a grapiprant clinical trial involving client-owned dogs with osteoarthritis receiving either placebo (n=131) or grapiprant (n=131) at 2 mg/kg daily for 28 days indicated a higher incidence of adverse drug events in the grapiprant group. However, these events were not serious; the most common were vomiting (24% with grapiprant versus 9% with placebo), diarrhea or soft stool (17% versus 13%), anorexia (9% versus 7%), and lethargy (6% versus 2%).[16] Similarly, according to the product package insert, among 366 client-owned dogs given 2 or 5 mg/kg q24h or 4 mg/kg q12h, the most common adverse events were intermittent diarrhea, vomiting, and anorexia. Serum alkaline phosphatase and alanine aminotransferase increased and total protein decreased with dose, but the dogs remained clinically normal.

Postmarket Surveillance

A third source of adverse drug event data is the FDA adverse event reporting site. The proportion of the most common adverse events (the number of times the event was reported divided by the total number of reports for that drug) was determined for grapiprant and then compared with the same events reported for deracoxib (**TABLE 1**). Of the approximately 2300 reports for grapiprant, the most common adverse events were diarrhea (31%) and vomiting (22%). The incidence of serious adverse events was consistently (numerically) lower than that for deracoxib. However, these data do not account for differences in the number of dogs in the United States who received either drug.

Grapiprant is a sulfa drug, as are many NSAIDs approved for use in dogs, but unlike sulfonamide antimicrobials, grapiprant does not contain an arylamine.

Grapiprant is a sulfa drug, as are many NSAIDs approved for use in dogs, but unlike sulfonamide antimicrobials, grapiprant does not contain an arylamine. As such, although allergies typical of sulfonamide antimicrobials are unlikely, adverse events associated with sulfa components may occur. Pork liver is added as a flavoring agent, which could potentially contribute to food allergies.

It is important to remember that even if grapiprant targets only EP_4 receptors, these receptors play roles at several other body sites. Thus, grapiprant use may lead to other adverse events.

DRUG INTERACTIONS

Two common pathways in drug, diet, or supplement interactions involve efflux transport proteins such as P-glycoprotein (MDR-1, ABCB-1) and CYP450 drug-metabolizing enzymes. According to the product package insert, grapiprant is a substrate for P-glycoprotein, which is present at portals of entry and tissue sanctuaries. As such, extra attention might be given to possible adverse drug events in breeds deficient in P-glycoprotein or if grapiprant is given with other medications known or suspected to interact with P-glycoprotein (e.g., cyclosporine, rifampin, imidazole antifungal drugs [ketoconazole, itraconazole, fluconazole]).[17]

The specific CYP450 enzymes responsible for metabolizing grapiprant have not been reported. However, the effects of other drugs that are broad inducers (e.g., phenobarbital, rifampin) or inhibitors (e.g., cyclosporine, chloramphenicol, imidazole antifungal drugs) of CYP450 enzymes[18] mandate extra attention to potential adverse drug events if used with grapiprant. Grapiprant does not seem to alter the metabolism of other drugs, including itself: the product

package insert indicates that in dogs, grapiprant is not an inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Furthermore, in beagles receiving either 6 or 50 mg/kg, grapiprant did not accumulate in plasma despite a 28-day treatment period.[8] As such, grapiprant probably can be safely combined with a variety of other drugs; however, more studies are needed.

SUMMARY

Overall, grapiprant may be useful for dogs with osteoarthritis. However, its relative efficacy compared with other NSAIDs has not yet been demonstrated.

- **Pharmacodynamics:** Grapiprant antagonizes EP_4 (highly selectively).
- **Pharmacokinetics:** Oral bioavailability is negatively affected by food and potentially by manipulation of the formulation; clearance decreases in a dose-dependent fashion.
- **Efficacy:** Research findings may suggest that the efficacy of grapiprant is less than that of other NSAIDs.
- **Safety:** Safety of grapiprant may be superior to NSAIDs but direct comparison studies are needed.
- **Adverse events:** Although grapiprant can lead to adverse events typical of NSAIDs, more serious adverse events are not common.
- **Drug interactions:** Drug interactions seem to be minimal, suggesting that grapiprant can be combined safely with most classes of non-NSAID analgesic drugs. Nonetheless, because the drug has been approved for only a short time, given that the EP_4 receptor plays a major role in the normal physiology of multiple organs (including the gastrointestinal tract and kidneys) and hemostasis, caution is recommended with its use, particularly in the presence of comorbidities.

More studies are needed to demonstrate the breadth of grapiprant's analgesic efficacy and to compare its safety with that of COX-2–targeting NSAIDs. To facilitate the generation of safety evidence, report adverse events (including therapeutic failure) to the manufacturer or FDA (fda.gov/animal-veterinary/safety-health). TVP

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Dr. Boothe received her DVM degree from Texas A&M in 1980, completed a small animal internship at Auburn University in 1980, received an MS degree from Texas A&M in 1985, completed a residency in small animal medicine in 1985, completed a PhrMA Fellowship in 1989, and received a PhD degree in 1989. In 1990, she joined Texas A&M in the Department of Veterinary Physiology & Pharmacology and became a professor. In 2003, she joined the Departments of Anatomy, Physiology and Pharmacology and Clinical Sciences at Auburn in 2003, where she directs the Clinical Pharmacology Laboratory. Dr. Boothe has authored or coauthored approximately 125 peer-reviewed scientific publications, 60 book chapters, and 2 textbooks. She received the Texas A&M University Achievement Award in Teaching, the Jack Mara Scientific Achievement Award for contributions in clinical pharmacology of the critical care patient, Auburn University Outstanding Graduate Student Mentor Award, the Zoetis Award for Excellence in Research, and an Alumni Professorship.