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WORDS OF CAUTION
Alprazolam
Lisa Radosta, DVM, DACVB

THERAPEUTICS SNAPSHOT
Cefpodoxime
Jennifer Schissler Pendergraft, DVM, MS, DACVD

RED LIGHT, GREEN LIGHT
Inflammatory Bowel Disease with Concurrent Pancreatitis
Julie Allen, BVMS, MS, DACVIM [Small Animal]

Rx SOLUTIONS
Which Drugs Can Be Used for Osteoarthritis in Dogs?
Kelley Thieman Mankin, DVM, MS, DACVS [Small Animal]
Alprazolam is generally safe to use in companion animals; however, behavioral and medical side effects and adverse events can occur.

**Side Effects & Adverse Events**

*Common side effects associated with alprazolam administration include:
- Ataxia
- Diarrhea
- Disinhibition
- Increased appetite
- Paradoxical excitement
- Sedation
- Vomiting

*In animals, physiologic tolerance can occur and possibly lead to rebound and/or withdrawal signs when alprazolam is discontinued. Rebound effects may include recurrence of original signs for which the medication was chosen (e.g., anxiety, phobia).
- In humans, signs of withdrawal include seizures, irritability, anxiety, panic attacks, and tension.

**Precautionary Measures**

*Use caution in patients receiving medications that impair or induce oxidative metabolism by the cytochrome P450 3A4 enzyme, including:
- Antifungals (e.g., ketoconazole, itraconazole)

*Certain antibiotics (e.g., doxycycline)
- Certain anticonvulsants (e.g., phenobarbital)

*Gradual decrease of alprazolam over 2 weeks is recommended for animals that have been treated daily for ≥14 days.

*Alprazolam treatment for aggression is controversial because of potential risk for disinhibition.
- Patients presented for aggression should be closely monitored for irritability and worsening of aggressive signs.

*Certain nutraceuticals and natural substances (e.g., St. John’s wort, valerian root) may decrease serum alprazolam levels by induction of CYP3A4 and increase CNS depression.
- Administer these substances with caution in patients receiving alprazolam.

*Doses may need to be decreased in older patients or those with impaired hepatic or renal function.

**Overdose Toxicity**

*Clinical signs of accidental overdose in dogs typically develop 10–30 minutes after ingestion and include:
- Ataxia
- Depression
- Diarrhea
- Disorientation
- Hyperactivity
- Hypothermia
- Increased salivation
- Tachycardia
- Tachypnea
- Tremors
- Vocalization
- Vomiting
- Weakness

*Treatment

*Induce vomiting (if <3 hours post-ingestion) and provide supportive care.
- In severe cases, flumazenil (benzodiazepine receptor antagonist) can be used.

**Do Not Use**

*Based on evidence of placental passage in animals and breast milk passage in humans, alprazolam should be avoided in pregnant or lactating animals.
Because of increased risk for narrow-angle glaucoma in at-risk humans, do not use alprazolam in animals with glaucoma.3,6-8

When prescribing controlled or other substances with potential for abuse by humans, veterinarians should monitor the accuracy of their prescriptions and verify that requested refills are in agreement with dosing.

Patients presented for aggression should be closely monitored for irritability and worsening of aggressive signs.1

REFERENCES

LISA RADOSTA, DVM, DACVB, is owner of Florida Veterinary Behavior Service in Jupiter. Dr. Radosta has authored textbook chapters, writes for Palm Beach Post, and podcasts CE for VetGirl. Her publications include research papers on thyroid disease and clinician–client communication. Dr. Radosta lectures nationally and internationally, is behavior section editor for Small Animal Advances in Medicine and Surgery, and is on the AAHA Behavior Management Guidelines task force and Fear Free advisory board. She completed her residency in behavioral medicine at University of Pennsylvania, where she received two national research awards.

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Cefpodoxime proxetil is an oral third-generation cephalosporin approved for treatment of skin infections in dogs.

Clinical Applications

The bactericidal spectrum for cefpodoxime proxetil involves both gram-positive cocci and gram-negative bacilli.

- Spectrum for gram-positive cocci includes methicillin-susceptible *Staphylococcus* spp and group G β-hemolytic *Streptococcus canis*.¹
- Spectrum for gram-negative bacilli includes *Proteus mirabilis*, *Pasteurella multocida*, and *Escherichia coli*.¹

In dogs, cefpodoxime treatment is most commonly prescribed for regional or generalized *Staphylococcus pseudintermedius* bacterial folliculitis.

- Staphylococcal pyoderma is most commonly observed in patients with cutaneous hypersensitivity disorders.

Given the gram-negative spectrum of cefpodoxime, its use as a first-tier antimicrobial for cutaneous staphylococcal infections is controversial.

- Individual and population selection for antimicrobial-resistant flora may occur, particularly extended-spectrum β-lactamase-resistant *E coli*.²
- In the author’s opinion, administration of cefpodoxime should be limited to cases that require less frequent dosing to ensure compliance or in patients with mixed infections that require the extended gram-negative spectrum of cefpodoxime.

The bactericidal spectrum for cefpodoxime treatment of skin infections in dogs ranges from gram-positive cocci to gram-negative bacilli.
Protocol & Side Effects

**Cefpodoxime is dosed at 5–10 mg/kg PO q24h.**¹
- Once-daily dosing promotes client compliance.
  — Can administer with food to ease patient dosing
- Treatment for 1 week beyond clinical resolution, along with adjunct topical antimicrobial therapy, is recommended for patients with staphylococcal bacterial folliculitis.²,³

The most commonly observed side effects—vomiting and diarrhea—reportedly occur in less than 5% of patients.⁴
- β-lactams have been implicated in canine cutaneous drug eruptions⁵ that may occur up to 2 weeks after treatment initiation.
  — The true prevalence of cutaneous adverse drug reactions in dogs (and cats) is presently unknown for any antibiotic, as it is likely that these drug eruptions are underreported.⁶

Precautionary Measures

**Conducting bacterial culture and sensitivity testing is recommended before cefpodoxime administration to patients that**
- Failed to respond to empiric antimicrobial therapy
- Have an extensive antimicrobial history
- Had a previous multidrug-resistant infection
- Cohabitate with an individual (human, animal) that has a confirmed multidrug-resistant infection
- Have a clinical diagnosis of deep pyoderma

**In consideration of the worldwide presence of canine methicillin-resistant staphylococci, a recheck examination must be performed in all patients before discontinuation of cefpodoxime.**
- Lack of improvement or development of new cutaneous lesions during cefpodoxime therapy should prompt examination and consideration for the presence of resistant infection or cutaneous drug eruption.

REFERENCES


JENNIFER SCHISSLER PENDERGRAFT, DVM, MS, DACVD, is assistant professor of veterinary dermatology at Colorado State University with a teaching (James L. Voss Veterinary Teaching Hospital), clinical, and research appointment. Her research efforts focus on staphylococcal infections, infection control, antimicrobial resistance, canine immunology, canine atopic dermatitis, and otology. After Dr. Pendergraft earned her DVM from Colorado State University, she completed a combined MS and dermatology residency program at The Ohio State University.
The following capsules provide brief overviews of key therapeutics studies explored in leading scientific journals.

**Bacterial Infection Treatment for Cats**

Pradofloxacin, a new third-generation oral fluoroquinolone, has lower in vitro minimum inhibitory concentrations against gram-positive aerobic bacteria and anaerobes. It is also active against *Bartonella henselae, Pasteurella multocida, Bordetella bronchiseptica*, extraintestinal *Escherichia coli*, and some mycobacterial species. Its dual-target mechanism of action may make it less likely than other fluoroquinolones to select for bacterial mutations.


**Efficacy of Pamidronate on Cancer Cells**

Pamidronate, an amino bisphosphonate, was used to investigate its in vitro effects on cancer cell lines and palliation in cats with nonresectable skeletal tumors. In vitro, pamidronate decreased feline cancer cell proliferation. Pamidronate can be administered practically in a clinical setting; however, because it was used as part of multimodal treatment, clinical response and pain control could not be attributed to pamidronate alone.


**Carprofen Unbound**

Unbound carprofen concentrations in canine interstitial fluid (ISF) were measured using in vivo ultrafiltration, and pharmacokinetic parameters of free carprofen concentrations in inflamed and normal control tissue sites were compared. Results indicated that (1) in vivo ultrafiltration techniques may be reliable for measuring unbound carprofen in ISF, (2) unbound drug disposition into tissue from unbound plasma drug concentrations is greater than predicted, and (3) minimal differences exist in drug concentrations and pharmacokinetic parameters between inflamed and uninflamed tissues.


**FIV as a Study of HIV**

Feline immunodeficiency virus (FIV) has been used as a model to study human immunodeficiency virus (HIV) and latent HIV reservoirs. In this study, chronically FIV-infected aviremic cats were treated with oral histone deacetylase inhibitor (HDACi) suberoylanilide hydroxamic acid (SAHA) to induce latent viral reactivation. Results suggested in vivo induction of viral transcriptional reactivation.

**Role of Mesenchymal Stromal Cells in New Drug Development**

Mesenchymal stromal cells (MSCs) have been proposed as vehicles for delivering anticancer agents, as they are simple to isolate, are present in many different mammalian tissues, and are able to hone in on the tumor microenvironment. In this study, MSCs primed with paclitaxel (a chemotherapeutic agent) demonstrated significant antiproliferative activity when tested in vitro on a human pancreatic cell line. These results suggested that MSCs might be used to package and deliver drugs for more targeted cancer therapy.


**Drug Resistance & Canine Hemangiosarcoma**

Canine hemangiosarcoma is poorly responsive to conventional chemotherapy. Progenitor cell populations from hemangiosarcoma lines grown as nonadherent sphere cell populations were found to contain subpopulations of drug-resistant cells. New treatment approaches may be utilized from this method of identifying the mechanisms that sphere cells use to elude cytotoxic drugs.


**Effects of Antacids on Serum Gastrin Levels**

Histamine type 2 (H2) receptor antagonists and proton pump inhibitors are known to induce hypergastrinemia during use. This randomized crossover study investigated how soon serum gastrin levels returned to baseline after 7 days of treatment with omeprazole and famotidine. Serum gastrin levels were analyzed during and after drug administration. Results showed serum gastrin levels decreased to baseline after a 7-day withdrawal period. Although recommended in human medicine, measuring serum gastrin levels after a 14-day withdrawal period does not appear necessary in dogs.


**Doxorubicin & Etoposide Effects on Feline Injection Site Sarcoma**

This study evaluated the cytotoxic effects of doxorubicin and etoposide used alone and in combination on a feline injection site sarcoma (FISS) cell line. Doxorubicin has previously been shown to delay the recurrence of FISS, but etoposide has not yet been studied in cats. Both drugs, when used as a single agent or together, significantly inhibited growth and promoted apoptosis of the FISS cell line.

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Inflammatory Bowel Disease with Concurrent Pancreatitis

PEPPER, A 7-YEAR-OLD, CASTRATED MINIATURE SCHNAUZER, presented with a history of inflammatory bowel disease (IBD) involving the stomach and duodenum for which he had been receiving prednisone at 0.5 mg/kg q48h. Overall, Pepper was doing well, with no ongoing vomiting or diarrhea, but he had been losing weight and previous laboratory work revealed fasting hyperlipidemia. At presentation, Pepper had a 24-hour history of acute bilious vomiting and mucoid diarrhea with hematochezia. Examination revealed a slight fever and cranial abdominal pain. Laboratory abnormalities included an inflammatory leukogram, moderately increased ALP, mild hypercholesterolemia, and considerable hypertriglyceridemia. A Spec cPL (IDEXX) assay was elevated at a concentration consistent with pancreatitis. Abdominal ultrasonography revealed a markedly hypoechoic left pancreatic limb. Working differentials were IBD, likely primary hyperlipidemia, and probable pancreatitis.

Which of the following medications would be appropriate?

Based on the information provided, how would you grade the following drugs and why?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Red</th>
<th>Yellow</th>
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<tbody>
<tr>
<td>Prednisone</td>
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<tr>
<td>Azathioprine</td>
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<td>Cyclosporine</td>
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<tr>
<td>Enrofloxacin</td>
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</table>

ALP = alkaline phosphatase, IBD = inflammatory bowel disease
Did you answer?

The following represents the best responses based on drug metabolism, pharmacokinetics, species, diagnostic differentials, clinical and laboratory data, and other pertinent findings.

**Prednisone**

Prednisone, a steroid with antiinflammatory and immunomodulatory properties, is the drug of choice for IBD, but steroids have long been cited as a possible cause of pancreatitis.\(^1\) Some studies looked mainly at changes in amylase and lipase, however, so it was believed that although steroids were increasing lipase values, they were not necessarily causing pancreatitis.\(^2\) In fact, there is some debate that steroids may be helpful in certain patients with chronic pancreatitis, particularly those with concurrent IBD. Of note, a recent population-based case-control study in humans suggested that steroids are indeed associated with increased risk for acute pancreatitis.\(^3\)

**Azathioprine**

Azathioprine, a purine analog immunosuppressant, has been used successfully in the management of IBD.\(^4\) However, this drug has been implicated as a cause of pancreatitis in humans and would not, therefore, be recommended for this patient.\(^5\)

**Cyclosporine**

Cyclosporine, a calcineurin inhibitor that suppresses the immune system primarily by inhibiting T lymphocytes, has been used in patients with refractory IBD.\(^6\) Ongoing research at Texas A&M University is investigating its use in dogs with insulin-resistant diabetes mellitus and chronic pancreatitis.\(^7\) There is some evidence in the human literature that chronic pancreatitis may have an underlying immune-mediated cause, which has also been the proposed etiology in English cocker spaniels afflicted with pancreatitis.\(^8\) While evidence is insufficient to recommend routine use of cyclosporine in dogs with pancreatitis, transition from prednisone to cyclosporine might be beneficial to control the IBD in this patient, with appropriate vigilance for the many potential drug interactions as characterized by cyclosporine.

**Carprofen**

Steroids and NSAIDs should never be administered concurrently because of the increased risk for GI bleeding, which may be increased further by existing impaired perfusion in the GI tract of patients with pancreatitis.\(^9\)
Fentanyl

Pain control is very important in the management of pancreatitis. Although traditionally there was concern that opioids induced “spasm” of the sphincter of Oddi, no study or evidence has indicated that fentanyl is contraindicated in patients with pancreatitis.10

Metoclopramide

Metoclopramide, a dopamine antagonist, is both an antiemetic and a prokinetic drug. However, dopamine may actually be helpful in both ameliorating pancreatic inflammation and improving pancreatic perfusion; therefore, the use of metoclopramide may be detrimental.11 In addition, more effective antiemetics are available, including ondansetron, dolasetron, and maropitant. Maropitant may also have beneficial antiinflammatory and analgesic effects because of its actions on substance P.12

Fish oil

Although it may seem counterintuitive in hyperlipidemic patients, fish oil products (particularly those high in omega-3 fatty acids) may reduce serum triglyceride concentrations by decreasing the synthesis of very low-density lipoproteins (VLDLs).13 Studies in humans with ulcerative colitis, Crohn’s disease, and pancreatitis have also suggested that because of their antiinflammatory properties, fish oils may be beneficial, although the results have been controversial. No studies in veterinary medicine have assessed the efficacy of fish oil in patients with IBD or pancreatitis.13-15

Chitosan

Chitosan, a form of fiber derived from shellfish, essentially acts as a fat sponge in the intestinal tract and can therefore be effective in the management of hyperlipidemia. There are no controlled studies evaluating its efficacy, but in general it is considered fairly safe. At high doses, deficiencies of fat-soluble vitamins and minerals may occur.16

IBD = inflammatory bowel disease, VLDL = very low-density lipoprotein
Metronidazole | CORRECT RESPONSE

Metronidazole, a nitroimidazole antibiotic believed to have immunomodulatory properties, has often been used as adjunct therapy for IBD, although one study revealed no difference in response to prednisone alone versus prednisone and metronidazole.\(^1\) Recent studies have suggested that long-term or high-dose use may lead to DNA damage, so courses should be limited.\(^2\) In addition, several case reports in the human literature have suggested that metronidazole may increase the risk for acute pancreatitis.\(^3\)

Enrofloxacin | CORRECT RESPONSE

Although enrofloxacin penetrates the pancreas well, the debate remains whether this drug is beneficial in patients with pancreatitis. Antibiotic coverage for enteric bacteria may be warranted if the patient is febrile, has toxic changes, and/or has evidence of GI mucosal barrier compromise. Infectious complications are rare in dogs as compared with humans. One experimental study in dogs suggested possible improvement in patient survival with antibiotic therapy, but only when given via the cranial mesenteric artery.\(^4\) Human literature wavers as to whether antibiotic therapy benefits these patients. No clinical studies have investigated the effect of antibiotics in dogs with pancreatitis.

**IBD** = inflammatory bowel disease


MORE on page 22 ➤

Non-steroidal anti-inflammatory drug
For oral use in dogs only

**BRIEF SUMMARY:**
Before using quellin soft chewable tablets, please consult the product insert, a summary of which follows:

**CAUTION:** Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

**PRODUCT DESCRIPTION:** quellin (carprofen) is a non-steroidal anti-inflammatory drug (NSAID) of the propionic acid class that includes ibuprofen, naproxen, and ketoprofen.

**INDICATIONS:** Carprofen is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

**CONTRAINDICATIONS:** Carprofen should not be used in dogs exhibiting previous hypersensitivity to carprofen.

**WARNINGS:** Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. For use in dogs only. Do not use in cats. All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered.

**PRECAUTIONS:** As a class, NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Effects may result from decreased prostaglandin production and inhibition of the enzyme cyclooxygenase which is responsible for the formation of prostaglandins from arachidonic acid. When NSAIDs inhibit prostaglandins that cause inflammation they may also inhibit those prostaglandins which maintain normal homeostatic function. These antiprostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease more often than in healthy patients. Carprofen is an NSAID, and as with others in that class, adverse reactions may occur with its use. The most frequently reported effects have been gastrointestinal signs, vents involving suspected renal, hematologic, and neurologic, dermatologic, and hepatic effects have also been reported. Concomitant use of carprofen with other anti-inflammatory drugs, such as other NSAIDs or corticosteroids, should be avoided because of the potential increase of adverse reactions, including gastrointestinal ulcerations and/or perforations. Carprofen is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. The safe use of carprofen in animals less than 6 weeks of age, pregnant dogs, dogs used for breeding purposes, or in lactating bitches has not been established.

**ADVERSE REACTIONS:**
During investigational studies for the caplet formulation with twice-daily administration of 1 mg/lb., no clinically significant adverse reactions were reported. Some clinical signs were observed during field studies which were similar for carprofen caplet and placebo treated dogs. Incidences were observed in both groups: vomiting (4%), diarrhea (4%), changes in appetite (3%), lethargy (1.4%), behavioral changes (1%), and constipation (0.3%).

For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

ANADA 200-555 Approved by FDA

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Which Drugs Can Be Used for Osteoarthritis in Dogs?

Kelley Thieman Mankin, DVM, MS, DACVS (Small Animal)
Texas A&M University

As mainstay treatment for osteoarthritis (OA), NSAIDs inhibit one or more steps in arachidonic acid metabolism, including inhibition of prostaglandins by cyclooxygenase (COX).

**COX Isoforms**
- COX-1 and COX-2 are known isoforms; COX-3 was recently recognized.1
  - COX-1 catalyzes formation of constitutive prostaglandins.2
  - COX-2 appears to catalyze formation of induced prostaglandins expressed in damaged or inflamed tissue.2
    - Also involved in pain response to injury
  - Recently COX-3, a brain-specific COX-1 variant, was identified in dogs.3
    - Preferentially inhibited by acetaminophen

**Inhibition of COX-2**
- Thought to supply desired benefits of NSAID administration by
  - Inhibiting induced prostaglandins
  - Avoiding unwanted NSAID side effects of inhibiting constitutive prostaglandins

**Recent studies**
- COX-2 may have some activity in constitutive prostaglandins, and COX-1 may have some activity in induced prostaglandins.4,5
  - COX-1 and COX-2 inhibition, therefore, is not clear-cut.4,5
    - In addition, little difference in improvement of clinical signs has been detected in studies comparing different NSAIDs with different COX-2 selectivity as administered to large groups of dogs.4
  - One NSAID may work better than another for an individual dog, with different classes of NSAIDs having different side effect profiles.6

**Carprofen**
- Carprofen, one of the first COX-2 preferential NSAIDs approved for dogs, has been shown to be effective treatment for canine OA.7-9

**Formulation**
- Oral, injectable

**Dose**
- 4.4 mg/kg q24h or divided 2.2 mg/kg q12h6,10

**Key Points**
- Dose-dependent side effects include
  - Anorexia, vomiting, diarrhea
  - In dehydrated or older dogs, renal decompensation11

ALT = alanine aminotransferase, COX = cyclooxygenase
• Idiosyncratic hepatotoxicity associated with markedly increased serum ALT occurs less commonly but can lead to acute hepatic failure.\(^{12}\)
  — Reported more commonly in the Labrador retriever as compared with other breeds\(^{12}\)

**Meloxicam**

Clinical trials have shown meloxicam to be effective treatment for OA in dogs.\(^{13-15}\)
Like carprofen, meloxicam preferentially inhibits COX-2.

**Formulation** → Oral (tablet or liquid), injectable

**Dose** → 0.1 mg/kg q24h\(^{6,10}\)

**Key Points**

• Like carprofen, most commonly reported side effects are
  — Anorexia, vomiting, diarrhea\(^{14}\)
• The following severe adverse events can occur with meloxicam administration
  — Hepatotoxicity\(^{10,16}\)
  — GI ulceration, including perforating ulcers\(^{10,17}\)

**Deracoxib**

Deracoxib, a COX-2 selective NSAID as compared with being COX-2 preferential, is labeled for treatment of canine OA.

**Formulation** → Oral (chewable tablet)

**Dose** → 1–2 mg/kg q24h\(^{6,10}\)

**Key Points**

• Approved for treatment of pain and inflammation associated with OA in dogs
  — Effective in controlling pain associated with induced synovitis\(^{18,19}\)
  — Clinical trials have shown that deracoxib is effective at improving signs associated with OA\(^{20,21}\)
• When administered at doses higher than labeled, dogs reportedly developed kidney abnormalities.\(^{22}\)
• **Caution/Warning**
  — While no kidney problems have been reported in dogs receiving the recommended dose, deracoxib should be used with caution in dogs with renal disease.

The NSAIDs presented here have all been approved for use in dogs with osteoarthritis and/or associated clinical signs.
— Has been associated with GI ulceration and perforation, particularly with administration of higher than recommended doses or in combination with another NSAID or glucocorticoid.\textsuperscript{23,24}

### Firocoxib

Firocoxib, approved for treatment of canine OA, is a COX-2 selective NSAID shown to be effective in treating pain and inflammation associated with induced synovitis.\textsuperscript{8}

**Formulation** → Oral (chewable tablet)

**Dose** → 5 mg/kg q24h\textsuperscript{6,10}

**Key Points**

- In a study comparing firocoxib with carprofen, fewer dogs experienced health problems with firocoxib than with carprofen.\textsuperscript{9}
- The most frequent side effects are vomiting and decreased appetite.  
  — Margin of safety is narrow in puppies.
- **Label Warning**  
  — Using doses higher than recommended in puppies younger than 7 months of age has been associated with serious complications, including hepatic abnormalities and decreased weight gain.

### Chondroprotectants

**Chondroitin Sulfate–Glucosamine Hydrochloride–Manganese Ascorbate**

Chondroitin sulfate–glucosamine hydrochloride–manganese ascorbate is proposed to reduce clinical signs of OA and slow or prevent progression of the degenerative process.

**Formulation** → Oral (chewable tablet)

**Dose** → Varies based on dog’s weight; refer to product label for recommended initial and maintenance dose schedules for joint disease in dogs

**Key Points**

- Glucosamine hydrochloride and chondroitin sulfate have been shown to accumulate in plasma after multiple doses and to have substantial carryover effect.\textsuperscript{25}
- This drug combination can produce beneficial effects in vitro, protect against synovitis,\textsuperscript{26} slow the degenerative process,\textsuperscript{27} and modulate metabolism of articular cartilage.\textsuperscript{28}
- When administered to dogs in vivo, results have not been as promising.  
  — One clinical study in dogs showed no improvement in objective gait analysis or subjective analysis by owner or orthopedic surgeon during the study period.\textsuperscript{13}
  — Ground reaction forces measured before and after were not significantly improved.

---

ASU = avocado/soybean unsaponifiables, COX = cyclooxygenase, HA = hyaluronic acid, IL = interleukin, MMP = matrix metalloproteinase, TGF = transforming growth factor
Glucosamine Hydrochloride–Chondroitin Sulfate–Avocado/Soybean Unsaponifiables

The combination of glucosamine hydrochloride–chondroitin sulfate–avocado/soybean unsaponifiables (ASU) is similar to chondroitin sulfate–glucosamine hydrochloride–manganese ascorbate and likewise is purported to reduce clinical signs of OA and slow or prevent progression of the degenerative process.

**Formulation** → Oral (chewable tablet)

**Dose** → Varies based on dog’s weight; refer to product label for recommended initial and maintenance dose schedules for joint disease in dogs

**Key Points**
- Numerous research studies have shown that ASU can decrease inflammation at the cellular level, decrease cartilage degradation, and promote cartilage repair.29-31
  - Can partially reverse the effects of IL-1 on chondrocytes and decrease matrix metalloproteinase (MMP) production, decreasing inflammation and cartilage degradation29,30
  - Can increase expression of TGF-β, suggesting stimulation of cartilage repair31,32
- An experimental study evaluating ASU administered to dogs with transected cranial cruciate ligaments found reduced development of cartilage and subchondral bone lesions.33
  - Study authors suspected that ASU worked by inhibiting nitric oxide synthase and MMP-13.33

Hyaluronan

Hyaluronan, also known as hyaluronic acid (HA), is a polysaccharide found in many tissues. HA is concentrated in synovial fluid, where its major function is to bind water and lubricate joints.

**Formulation** → Injection (intraarticular)

**Dose** → Using high molecular weight hyaluronan compound, 10 mg weekly34-36; in *Plumb’s Veterinary Drug Handbook*, 3–5 mg/kg weekly also recommended for adjunct treatment of synovitis
- Follow aseptic technique

**Key Points**
- Most commonly administered directly into the joint.
  - By this route, HA has been shown to improve gait function in OA mouse models.37
- In human studies, intraarticular HA improved viscoelasticity, provided antiinflammatory activity, provided analgesia, and decreased degradation of articular cartilage.38,39
- Studies showed no clinical improvement or prevention of OA when administered to dogs with transected cranial cruciate ligaments.34-36,40

Avocado/soybean unsaponifiables can decrease inflammation and cartilage degradation and promote cartilage repair.29-31
***Chondroprotectants***

**Polysulfated Glycosaminoglycan**

Polysulfated glycosaminoglycan (PSGAG) is labeled as a disease-modifying OA supplement purported to slow OA development and diminish associated clinical signs.

**Formulation** → Injection (IM)
- For treatment of noninfectious, traumatic, or degenerative arthritis

**Dose** → 4.4–5 mg/kg IM twice weekly for 4 weeks (recommended)

**Key Points**
- In one study, 75% of dogs had significantly improved lameness scores after treatment with PSGAG.
- Potential use in inhibiting cartilage matrix degradation
  - Full mechanism of action is unknown but has been shown to decrease COMP (cartilage oligomeric matrix protein), a substrate for catabolic MMP enzymes.
- May increase synthesis of collagen (in vitro)
- Young puppies treated with PSGAGs showed less hip subluxation than did untreated puppies.
- **Warning**
  - Similar in structure to heparin and should not be used in dogs with coagulation abnormalities

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***Analgesics***

**Tramadol**

Tramadol is a central-acting synthetic opiate-like (mu-receptor) agonist. Its mechanism of action involves numerous metabolites.

**Formulation** → Oral (tablet)

**Dose** → 4–10 mg/kg q8h

**Key Points**
- Now a class IV schedule drug
- In part, analgesia may be achieved because tramadol and its metabolites are opiate-like mu-receptor agonists.
  - Because of how dogs metabolize tramadol, they are not expected to experience substantial opioid effects.
  - Mechanism of action in dogs likely results from metabolites acting as serotonin and norepinephrine reuptake inhibitors.
- Shown to be effective in alleviating clinical signs of OA in dogs
- Sedation most common side effect; dogs may develop decreased bioavailability over time (ie, tramadol may undergo decreased absorption with multiple doses).
- Evidence that tramadol alone has a detrimental effect on gastric barrier function is lacking.
- **Caution**
  - Dose adjustments may be required in dogs with impaired renal or hepatic function.
Gabapentin & Pregabalin

Both gabapentin and pregabalin were developed as antiepileptic drugs but have been used for treatment of chronic pain.46

Formulation → Oral (liquid or capsule)

Dose recommended (empiric) for gabapentin → 10–20 mg/kg q8h46

Dose recommended for pregabalin → 4 mg/kg q12h46

Key Points

• Both are alkylated analogs of gamma-aminobutyric acid (GABA).
  — Believed to work by blocking voltage-gated calcium channels, reducing neurotransmitter release, and attenuating postsynaptic excitability
  — Suspected neuropathic pain has been successfully treated with gabapentin.49
• Although both drugs are reportedly effective treatment for chronic pain in humans, no studies have evaluated gabapentin or pregabalin for management of canine OA.
  — Studies have shown no significant benefit to administration of gabapentin as an adjunct to other analgesics in dogs undergoing forelimb amputation or intervertebral disk surgery.50,51
• Caution
  — Gabapentin liquid contains xylitol; however, the concentration of xylitol in the liquid is low enough that routine dosing of gabapentin is unlikely to result in toxicity.46

Amantadine

Amantadine, first used as an antiviral medication against influenza in humans, is now primarily prescribed for pain relief in both human and veterinary medicine because of its ability to inhibit the N-methyl-d-aspartate (NMDA) receptor.

Formulation → Oral (liquid or tablet)

Dose (recommended) → 3–5 mg/kg q24h46

Key Points

• Should not be used as sole therapy for OA but should be combined with and may enhance the effects of NSAIDs, opioids, or gabapentin or pregabalin46
• Inhibits the NMDA receptor by encouraging channel closure and inhibiting NMDA responses
• In one study of dogs with OA pain refractory to NSAID treatment, addition of amantadine to NSAID therapy resulted in improved function, presumably because of pain relief.52
  — In the same study, no adverse effects or significant changes in laboratory results were detected.
Dried Milk Protein

- Collected from hyperimmunized cows; purported to contain factors that block cytokines and inhibit neutrophil participation in an inflammatory response
- One clinical trial reported improvement in clinical signs of OA.

Green-Lipped Mussel Extract

- Green-lipped mussel extract (GLME; *Perna canaliculus*) has improved clinical signs of canine OA.
  - Long-term administration may be required.
- How GLME exerts beneficial effects is unknown but suspected to be secondary to high concentrations of omega-3 fatty acids, which act as inhibitors of arachidonic acid metabolism by COX and lipoxygenase (LOX) pathways.
- Has been shown to have antiinflammatory effects.

Omega-3 Fatty Acids

- Supplementation may lead to decreased inflammation.
- Higher blood levels were detected in dogs fed diets supplemented with omega-3 fatty acids; owners reported improved mobility in arthritic pets.
- Supplementation may allow reduced NSAID dose.

S-Adenosyl L-Methionine

- *S*-adenosyl *L*-methionine (SAMe), a nutraceutical most commonly used to treat canine liver disease, has no reported side effects in dogs.
- SAMe has antioxidant properties that may benefit osteoarthritic joints but in one study was not an effective standalone treatment for reducing clinical signs of OA in dogs.

**REFERENCES**

7. **Long-term treatment with carprofen of...**


41. Novel animal health [product label]. Greensboro, NC.


Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. Each mL of this sterile product for injection contains meloxicam 5.0 mg, sodium chloride 150 mEq, sodium hydroxide 0.5%, glycerin 0.5% and meglumine 0.3%, in water for injection, pH adjusted with sodium hydroxide and hydrochloric acid.

**Indications:**
- Dogs: Meloxicam (meloxicam) Solution for Injection is indicated in dogs for the control of pain and inflammation associated with osteoarthritis.
- Cats: For the control of postoperative pain and inflammation associated with orthopedic surgery, urology/uroselective and castration when administered prior to surgery.

**Contraindications:**
- Dogs or cats with known hypersensitivity to meloxicam should not receive Metacam Solution for Injection. Additional doses of meloxicam or other NSAIDs in cats are contraindicated, as no safe dosage for repeated NSAID administration has been established.

**Precautions:**
- Patients at greatest risk for renal toxicity are those that are dehydrated, have moderate to severe renal function impairment, are receiving diuretics, or are administered prior to surgery.

**Adverse Reactions:**
- Dogs: A field study involving 224 dogs was conducted wherein 109 were administered meloxicam and 115 were administered a placebo. Based on the results of this study, G1 abnormalities, such as vomiting (3 dogs), diarrhea (2 dogs), soft feces (3 dogs), and anorexia (1 dog) were noted. The incidence of vomiting, diarrhea, and/or anorexia was lower in the meloxicam group and they resolved within 12 hours. No additional adverse events were noted.
- Cats: A field study involving 138 cats was conducted. Of the 66 cats that received Meloxicam Solution for Injection, a cats (8.3%) experienced post-treatment elevated serum blood urea nitrogen (BUN) levels. The pre-treatment values were in the normal range. Of the 66 cats in the butorphanol treatment group, no cats experienced post-treatment elevated serum BUN levels. New cat (2.5%) receiving Metacam Solution for Injection showed post-treatment anemia. Four cats (6.1%) in the butorphanol treatment group had post-treatment anemia. Twenty-four hours after the injection with Metacam Solution for Injection, one cat experienced pain upon palpation of the injection site. In studies used for the foreign approval of Metacam Solution for Injection in cats, lethargy, vomiting, inappetence, and transient pain immediately after injection were noted. Diarrhea and fecal occult blood have also been reported. Adverse reactions reported post-approval were: Urinary (azotemia, elevated creatinine, elevated phosphorus, renal failure), gastrointestinal (anorexia, vomiting, diarrhea), neurological/behavioral (laxity, depression), and hematomas (laxity). Acute renal failure and death have been associated with the use of meloxicam in cats.

**Information for Dog and Cat Owners:** Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with NSAID intolerance. Adverse reactions may include vomiting, diarrhea, lethargy, decreased appetite and behavioral changes. Do not repeat the single, one-time dose of meloxicam in cats or dogs. Owners should be advised to observe their dogs and cats for signs of potential drug toxicity.

**Manufactured by:**
- Boehringer Ingelheim Vetmedica, Inc. St. Joseph, MI 49085 U.S.A.
- US Patent 6,184,220

Metacam is a registered trademark of Boehringer Ingelheim Vetmedica GmbH, licensed to Boehringer Ingelheim Vetmedica, Inc.
D NEW | ALFAXALONE

The IV anesthetic Alfaxan\(^1,2\) (alfaxalone; Jurox, alfaxan.com), a neurosteroid that potentiates GABA in the CNS to cause general anesthesia, has been approved by the FDA as an injectable anesthetic agent for use in dogs and cats. Anesthesia can be induced with Alfaxan, followed by maintenance with an inhalant or CRI infusion. Alfaxan is a schedule IV controlled substance available in 10-mL single-use vials (10 mg/mL).\(^3\)

Sources
1. FDA Center for Veterinary Medicine, NADA #141-342, approval September 1, 2014.
3. alfaxan.com

D LABEL CHANGE | ONDANSETRON

The labeled risks for Zofran (ondansetron; GlaxoSmithKline) have been modified to include serotonin syndrome.\(^1\) Ondansetron is a 5-HT\(_3\) receptor antagonist used to treat patients with nausea and vomiting. Patients concurrently receiving other drugs that potentiate serotonin (eg, SSRIs, MAO inhibitors, tramadol, fentanyl, mirtazapine) may be at risk for serotonin syndrome.

Source
1. FDA.org, Zofran, Label and Approval History, letter dated September 18, 2014.

D LABEL CHANGE | TRAMADOL & HYDROCODONE

Pain medications containing tramadol\(^1\) & hydrocodone\(^2\) have been reclassified based on potential for abuse and addiction. The DEA has reclassified tramadol as a schedule IV controlled substance; hydrocodone is now labeled in the schedule II category. Prescribers should review DEA regulations for handling and prescribing both drugs (deadiversion.usdoj.gov/pubs/manuals/sec/message.htm).

Sources

D NEW RELEASE | OXYTETRACYCLINE

Terramycin\(^1,2\) ophthalmic ointment (oxytetracycline hydrochloride with polymyxin B sulfate; Zoetis, zoetis.com) has been reintroduced after being taken off the market for manufacturing disruptions. This broad-spectrum ophthalmic antibiotic ointment for use in dogs and cats with superficial ocular infections is distributed in 3.5-g tubes and available from multiple distributors as well as the manufacturer.

Sources

GABA = gamma-aminobutyric acid, MAO = monoamine oxidase, SSRI = selective serotonin reuptake inhibitor

KEY
D Drug
N Nutraceutical
T Therapeutic Diet
B Biologic

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And you can inject with confidence, because every vial of METACAM is backed by Boehringer Ingelheim Vetmedica, Inc.—a company you know and trust.

METACAM was the first NSAID injection approved for both cats and dogs in the US\(^1\) and has been trusted around the globe for more than a dozen years.\(^2\) A single preoperative injection controls postoperative pain in cats.\(^1\) Plus, an in-office injection of METACAM provides timely relief of pain and inflammation associated with osteoarthritis in dogs.

Try injectable METACAM for both dogs and cats. Even they can agree it’s the go-to treatment for pain and inflammation!

**IMPORTANT SAFETY INFORMATION:** Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats. Do not follow meloxicam injection in cats with any other NSAID. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, kidney, or liver side effects. The most common side effects of METACAM reported in field studies were vomiting and soft stool/diarrhea. Pets should be evaluated for pre-existing conditions and currently prescribed medications prior to and during treatment with METACAM. Concurrent use with another NSAID, corticosteroid, or nephrotoxic medication should be avoided. The safe use of METACAM in dogs younger than 6 months of age, cats younger than 4 months of age, dogs and cats used for breeding, or in pregnant or lactating female cats and dogs has not been evaluated. Please refer to the package insert for complete product information or visit www.metacam.com.