April/May 2021

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COMMON COMPLICATIONS OF TIBIAL PLATEAU-LEVELING OSTEOTOMY

IN THIS ISSUE

Volume 19 Number 3

WSAVA Global Veterinary Community

clinician's brief

THE OFFICIAL CLINICAL PRACTICE JOURNAL OF THE WSAVA

Trusted for Your Practice

- Designed with compliance in mind, *NexGard*® (afoxolaner) is a leader in **average number of months of oral flea and tick control product purchased per patient per year.***[1]
- More *NexGard* users purchased **a full 12 months of flea and tick protection** than users of any other flea and tick chew.*[1]

In Clinic. At Home.

NexGard® (afoxolaner) has you covered.

Thank you for trusting us over 270 million times.[3]

NexGard®
(afoxolaner) Chewables

IMPORTANT SAFETY INFORMATION: *NexGard* is for use in dogs only. The most frequently reported adverse reactions include vomiting, pruritus, lethargy, diarrhea and lack of appetite. The safe use of *NexGard* in pregnant, breeding, or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures or neurologic disorders. For more information, see the full prescribing information or visit NexGardClinic.com.

*Assessment was conducted by IDEXX® and leveraged veterinary clinic PIMS transaction level data for 2019. This analysis included data from approximately 7,000 U.S. clinics that had consistent data from 2017 to 2019. To be included, patients needed to have at least one parasiticide transaction in the baseline year (2018). The analysis was limited to loyal patients, where loyalty was defined as having one flea/tick control brand during the full three-year period. The average number of months of *NexGard* purchased per year was 6.64, compared to 6.69 for BRAVECTO. This analysis overestimates the duration of efficacy for BRAVECTO. For comparison purposes, each BRAVECTO chew was assessed as providing three months of flea & tick protection versus the labeled 12-week coverage for fleas and three species of ticks, and 8-week coverage for Lone Star ticks.

1. Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA. 2. Data on file at Boehringer Ingelheim. 3. Data on file at Boehringer Ingelheim.

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- **Only chew FDA-approved** to prevent Lyme infections by killing black-legged ticks.
- Safe for puppies as young as **8 weeks**, weighing as little as **4 pounds**.

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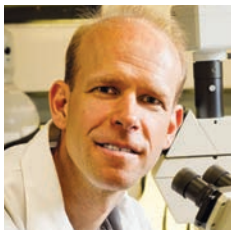

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Providing small animal practitioners and their teams with practical, relevant information on the latest topics in veterinary medicine

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CONSULT THE EXPERT PAGE 90

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PROCEDURES PRO PAGE 74

KARYN HARRELL, DVM, DACVIM, is an assistant clinical professor of internal medicine at North Carolina State University. She earned her DVM from Michigan State University, completed an internship at University of Minnesota, and completed a residency in internal medicine at North Carolina State University. Dr. Harrell is also director of the internship program at North Carolina State University and oversees the radioactive iodine treatment center at the veterinary hospital.

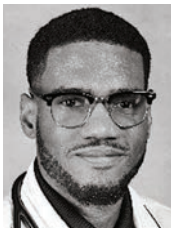
DIFFERENTIAL DIAGNOSIS PAGE 15

DIFFERENTIAL DIAGNOSIS PAGE 31

BARRY HEDGESPETH, BVSc, is a clinician investigator at North Carolina State University, where he recently completed a small animal internal medicine residency. He is now completing a PhD in immunology with a specific focus on mast cell biology and manipulation using splice-switching antisense oligonucleotides.

DIFFERENTIAL DIAGNOSIS PAGE 15

DIFFERENTIAL DIAGNOSIS PAGE 31



DOMINIQUE HEMMINGS, DVM, is a clinical instructor of small animal surgery at Tuskegee University, where he also completed a small animal rotating internship and a small animal surgical internship. He earned his DVM in 2016 from The University of the West Indies in St Augustine. Dr. Hemmings has a special interest in minimally invasive fracture repairs and multimodal approaches to pain control.

CONSULT THE EXPERT PAGE 19

AMY L. PIKE, DVM, DACVB, is owner of the Animal Behavior Wellness Center in Fairfax, Virginia. She earned her DVM from Colorado State University. Dr. Pike was a captain in the US Army Veterinary Corps and was responsible for US customs and border patrol horses as well as military working dogs. She has since worked exclusively in small animal practices, with intense focus on canine and feline behavior.

CASE IN POINT PAGE 83

SELENA TINGA, DVM, PhD, DACVS-SA, is a small animal orthopedic surgery faculty member at The Ohio State University. She earned her DVM from Cornell University and completed a small animal rotating internship at Texas A&M. She also completed a residency in small animal surgery and earned her PhD in canine stifle kinematics at University of Florida. Dr. Tinga has special interest in angular limb deformity correction.

CASE IN POINT PAGE 19

SCOTT WEESE, DVM, DVSc, DACVIM, is the editor in chief of *Clinician's Brief*. He is also the chief of infection control at Ontario Veterinary College in Ontario, Canada, and a veterinary internist and microbiologist. Dr. Weese's research interests are infectious and zoonotic disease, particularly of companion animals, as well as infection control, staphylococcal infections, *Clostridium difficile* infection, and antimicrobial therapy. He holds a Canada Research Chair in zoonotic disease.

DIAGNOSTIC TREE PAGE 26

NexGard®
(afoxolaner) Chewables

Brief Summary: Before using NexGard® (afoxolaner) Chewables, please consult the product insert, a summary of which follows.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: NexGard is a soft chewable for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg).

Indications: NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations *(Ctenocephalides felis),* and the treatment and control of *Ixodes scapularis, Dermacentor variabilis, Amblyomma americanum,* and *Rhipicephalus sanguineus* infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. NexGard is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Dosage and Administration: NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg). See full product insert for dosing table and details.

Warnings: Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately. Keep NexGard in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions: Afoxolaner is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated.

Adverse Reactions: In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table.

Table 1: Dogs with Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N[1]	% (n=415)	N[2]	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

[1] Number of dogs in the afoxolaner treatment group with the identified abnormality.

[2] Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

Post-Approval Experience (July 2018): The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events reported for dogs are listed in decreasing order of reporting frequency for NexGard: Vomiting, pruritus, lethargy, diarrhea (with and without blood), anorexia, seizure, hyperactivity/restlessness, panting, erythema, ataxia, dermatitis (including rash, papules), allergic reactions (including hives, swelling), and tremors.

Effectiveness: See full product insert for details regarding Effectiveness.

Animal Safety: In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose for a total of six treatments. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, no adverse reactions were observed from the concomitant use of NexGard with other medications.

Contact Information: For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

The information provided here is not comprehensive. The full FDA-approved product insert is available at www.nexgardfordogs.com. Consult your veterinarian for further information.

Product approved by FDA under NADA # 141-406

Marketed by: Frontline Vet Labs™, a Division of Boehringer Ingelheim Animal Health USA Inc. Duluth, GA 30096

NexGard® is a registered trademark and FRONTLINE VET LABS™ is a trademark of the Boehringer Ingelheim Group.

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Reference package insert: 1050-4493-09 Rev. 11/2019

Brief summary preparation date: 08/2020

US-PET-0735-2020

From *Clinician's Brief* on Social Media

WE ASKED . . .

Have you ever diagnosed gastric dilatation volvulus in a small-breed dog?

"Yes, in a dachshund."—*Dianne G*

"Not exactly a small breed, but I have seen it in a basset hound."—*Beth E*

"The first time I saw it was in a cat!"—*Kathleen S*

"Yes, in a shih tzu."—*Leslie H*

"A pug is the smallest I have seen that was confirmed."—*Linda S*

Do you prefer to vaccinate cats in the distal limbs or distal tail?

"Limbs—I cannot imagine injecting anything in a cat's tail."—*Aleksandra B*

"I had 2 cats that were both amputees. Vaccinating in the tail removes any concerns I had about vaccine-related sarcoma."—*Katy W*

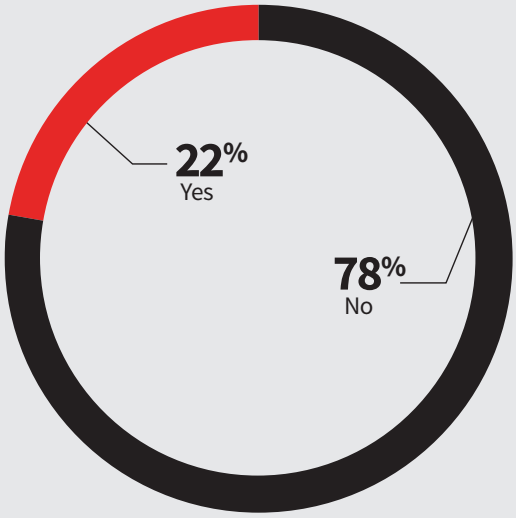
"I prefer the tail, unless the cat is fractious."—*Jeremy N*

"I prefer the distal limbs. I have never tried injecting a vaccine in the tail."—*Maheen M*

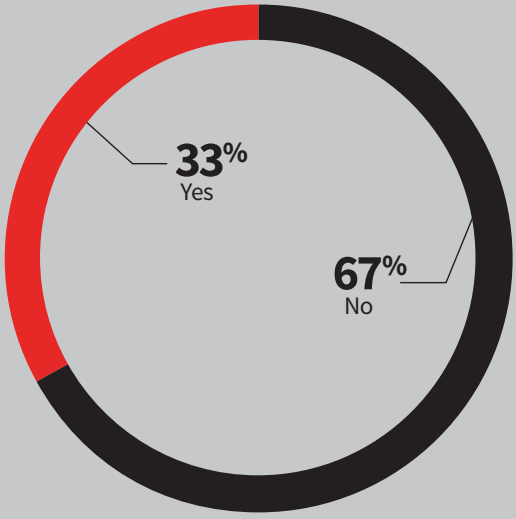
"I understand the reasoning, but a subcutaneous injection in the tail seems difficult."—*Hali H*

"Distal limb all the way!"—*Maude P*

Do you give your personal phone number or email to clients?



Do you use pimobendan in cats?



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RenalTech™ increases feline visits by 31%

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Hill's Prescription Diet Derm Complete is our masterpiece. The only clinically tested nutrition for **both food *and* environmental allergies** (among leading brands in North America).

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1. Manage itching in dogs with food and/or environmental allergies
2. Reduce licking, scratching, head shaking and skin redness in dogs with environmental allergies

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IN THIS ISSUE

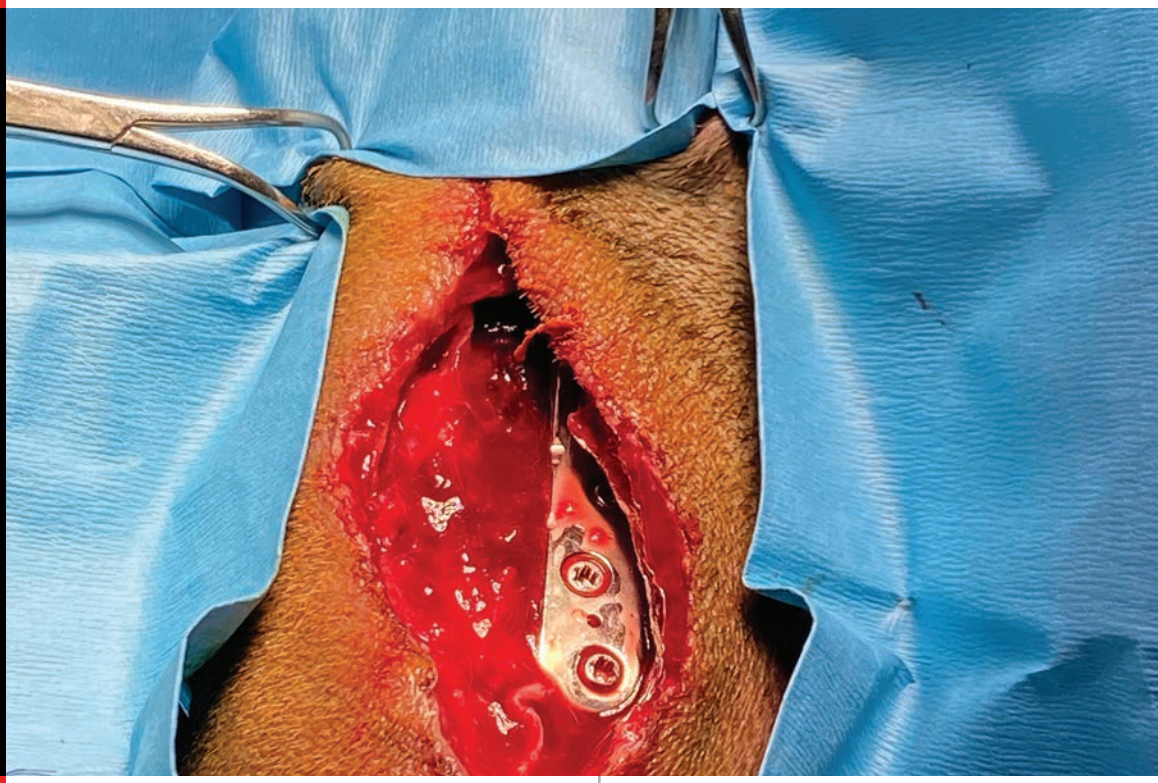
ON THE COVER

CONSULT THE EXPERT

Common Tibial Plateau-Leveling Osteotomy Complications

Dominique Hemmings, DVM
Selena Tinga, DVM, PhD, DACVS-SA

PG 19



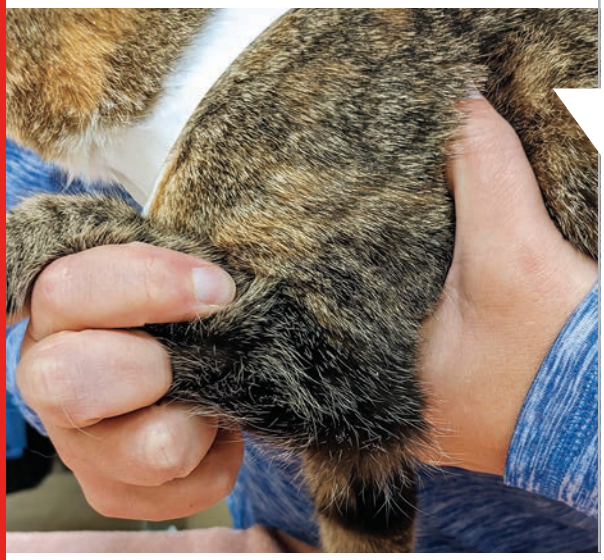
NOTICE OF CORRECTION

The article "Top 5 Situations for Judicious NSAID Use," published in the March 2021 issue of *Clinician's Brief*, contained 2 errors.

"Several studies evaluating renal function after NSAID administration as anesthesia have not found evidence of significant dysfunction …" should have read, "Several studies evaluating renal function after NSAID administration and anesthesia have not found evidence of significant dysfunction …"

"Because patients with existing renal disease may be at increased risk for hypotensive events, NSAIDs as anesthesia should not be used in these patients" should have read, "Because patients with existing renal disease may be at increased risk for AKI, NSAIDs should not be used during anesthesia for these patients."

A corrected version has been published online and can be found at **brief.vet/judicious_nsaid_use**. *Clinician's Brief* regrets the errors.



THE PROVEN WAY
TO TREAT CANINE DIABETES
ONCE-A-DAY

The breakthrough you've been waiting for is here: now you can deliver glycemic control in most diabetic dogs WITH A SINGLE DAILY INJECTION.[1,2] To learn more, contact your Boehringer Ingelheim Sales Representative or Professional Services Veterinarian.

ProZinc®
(protamine zinc recombinant human insulin)

*PROZINC is approved for twice-daily use in cats.[3]

IMPORTANT SAFETY INFORMATION: PROZINC is for use in dogs and cats only. Keep out of the reach of children. Animals presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking (dogs only), diarrhea, and ataxia. Many of the adverse reactions, such as lethargy, seizures, shaking (dogs only), and ataxia, are associated with hypoglycemia. Glucocorticoid and progestogen use should be avoided. The safety and effectiveness of PROZINC in puppies, kittens, or breeding, pregnant, and lactating animals has not been evaluated. PROZINC is contraindicated during episodes of hypoglycemia and in animals sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. **For more information, please see full prescribing information.**

References:
[1] Data on file at Boehringer Ingelheim.
[2] ProZinc® (protamine zinc recombinant human insulin) [Freedom of Information Summary]. Duluth, GA: Boehringer Ingelheim Animal Health USA, Inc.; 2019.
[3] ProZinc® (protamine zinc recombinant human insulin) [Freedom of Information Summary]. St. Joseph, MO: Boehringer Ingelheim Vetmedica, Inc.; 2009.

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Boehringer Ingelheim

See pages 10 and 11 for product information summary.

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THIS MONTH'S FEATURED CLINICAL CONTENT AVAILABLE ONLY ONLINE

CONTINUING EDUCATION

Updated: Canine Aggression

Whether directed at an owner, another dog, or the veterinary team, canine aggression can be resolved. This course can help tailor behavior modification for patient success and safety.

brief.vet/canine-aggression

QUIZ

Xenotransfusion in a Cat

Rebecca Smith, LVMT, VTS (ECC)
Adesola Odunayo, DVM, MS, DACVECC

brief.vet/xenotransfusion

Contact us at
editor@cliniciansbrief.com

Articles archived at
digital.cliniciansbrief.com

Package Insert for Dogs

ProZinc®
(protamine zinc recombinant human insulin)

40 IU/mL

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

Each mL contains:

recombinant human insulin	40 International Units (IU)
protamine sulfate	0.466 mg
zinc oxide	0.088 mg
glycerin	16.00 mg
dibasic sodium phosphate, heptahydrate	3.78 mg
phenol (added as preservative)	2.50 mg
hydrochloric acid	1.63 mg
water for injection (maximum)	1005 mg

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

Indication: PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.

Dosage and Administration: USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial. Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the dog.

Always provide the Client Information Sheet with each prescription.

Starting dose: The recommended starting dose for PROZINC is 0.2-0.5 IU insulin/pound of body weight (0.5-1.0 IU/kg) **once daily**. The recommended starting dose for naïve dogs is the lower end of the dose range. The recommended starting dose for dogs with poorly controlled diabetes mellitus and transitioning from another insulin product is the mid to higher end of the dose range based on the veterinarian's experience with the dog's medical history and previous insulin dose. When transitioning from another insulin, the dog's blood glucose and general condition should be closely monitored. **When transitioning from another insulin, PROZINC should be started once daily, regardless of the frequency of prior insulin use.**

The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the dog at appropriate intervals and adjust the dose and frequency based on both clinical signs and laboratory test results (the blood glucose curve values and shape, nadir, and fructosamine) until adequate glycemic control has been attained. In the effectiveness field study, glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 125 mg/dL, the maximum blood glucose was ≤ 300 mg/dL, and clinical signs of hyperglycemia such as polyuria, polydipsia, or weight loss were improved.

Changing to twice daily dosing: Twice daily dosing should be considered if the duration of insulin action is determined to be inadequate with once daily dosing. Use caution when adjusting from once daily to twice daily dosing because PROZINC may have prolonged duration of action in some dogs (see Clinical Pharmacology). The veterinarian should closely monitor the duration of action using blood glucose curves to avoid the increased risk of hypoglycemia. If twice daily dosing is initiated, the two doses should each be approximately 25% less than the once daily dose required to attain an acceptable glucose nadir. For example, if a dog receiving 10 units of PROZINC once daily has an acceptable nadir but inadequate duration of activity, the dose should be changed to 7 units twice daily (round down to the nearest whole unit).

Further adjustments in the dosage may be necessary with changes in the dog's diet, body weight, or concomitant medication, or if the dog develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

Contraindications: PROZINC is contraindicated in dogs sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

Warnings:
User Safety: For use in dogs and cats. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with running water for at least 15 minutes. Accidental injection may cause hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

Animal Safety: Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A dog with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic dogs that are difficult to regulate.

Precautions: Dogs presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating dogs has not been evaluated.

The safety and effectiveness of PROZINC in puppies has not been evaluated.

Adverse Reactions: In a 182-day field study, 276 dogs received PROZINC. The most common adverse reactions were lethargy, anorexia, hypoglycemia, vomiting, seizures, shaking, diarrhea, and ataxia.

Table 1 summarizes the adverse reactions reported in the study. Clinical signs of hypoglycemia varied and included seizure, collapse, ataxia, staggering, trembling, twitching, shaking, disorientation, lethargy, weakness, and vocalization. In Table 1, the individual clinical signs that were observed during the episodes of hypoglycemia are captured as separate adverse reactions and a single dog may have experienced more than one clinical sign of hypoglycemia.

Table 1. Adverse reactions seen in the safety population (276 dogs)

Adverse Reaction	Number and Percentage
Lethargy (lethargy, depression, listless, and tiredness)	45 (16.3%)
Anorexia (anorexia, decreased appetite, inappetence, and not eating)	28 (10.1%)
Hypoglycemia with clinical signs	24 (8.9%)
Vomiting	21 (7.6%)
Seizures	16 (5.8%)
Shaking/trembling/twitching	13 (4.7%)
Ataxia (ataxia, balance problem, stumbling gait)	11 (4.0%)
Diarrhea (includes bloody diarrhea)	9 (3.3%)
Disorientation/confusion	9 (3.3%)
Weakness	8 (2.9%)
Restlessness/anxiety/agitation	6 (2.2%)
Cataract	6 (2.2%)
Panting (panting and tachypnea)	6 (2.2%)
Hematuria	4 (1.5%)

Clinical pathology: The only change seen in complete blood count, serum chemistry, and urinalysis results was an elevation in mean cholesterol at Day 182 (432.6 mg/dL, normal range 131-345 mg/dL) compared to Day -1 (333.7 mg/dL).)

Injection site reactions: Seven dogs had injection site reactions, including observations of thickened skin, swelling, bumps at the injection site, and redness. All injection site reactions resolved without cessation of PROZINC therapy. Reaction to the injection, including vocalization, was observed in four dogs.

Hypoglycemia: There were 80 hypoglycemic episodes recorded during the study with some dogs experiencing more than one episode; 37 episodes were associated with clinical signs in 24 dogs, 40 episodes were without clinical signs in 27 dogs, and 3 were with unknown signs in 2 dogs. Clinical signs of hypoglycemia varied and included seizure, collapse, ataxia, staggering, trembling, twitching, shaking, disorientation, lethargy, weakness, and vocalization. Some dogs required hospitalization and intravenous dextrose while most recovered after receiving oral supplementation with a meal and/or oral glucose such as syrup. Two dogs were euthanized when the hypoglycemia did not resolve with supportive care. Hypoglycemia without clinical signs was defined as two consecutive blood glucose curve values < 60 mg/dL unaccompanied by clinical signs.

Diabetic ketoacidosis and pancreatitis: Eleven dogs were diagnosed with diabetic ketoacidosis. Four of these 11 dogs died or were euthanized, one after one dose of PROZINC. Twenty-one dogs were diagnosed with pancreatitis. Seven of these 21 dogs died or were euthanized due to complications of pancreatitis. Four dogs had concurrent diabetic ketoacidosis and pancreatitis, three of which died or were euthanized. Not all the deaths were considered related to PROZINC.

Deaths: Thirty-six (36) dogs died or were euthanized, six of which were possibly related to PROZINC. One dog died from recurrent episodes of pancreatitis, and one died after developing severe vomiting and diarrhea followed by a seizure. Four dogs were euthanized: one developed severe pancreatitis and azotemia, one had recurrent episodes of pancreatitis and diabetic ketoacidosis, and two for lack of effectiveness.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

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/reportanimalae.

Clinical Pharmacology: PROZINC was administered subcutaneously to 10 healthy Beagles using an incomplete crossover design at doses of 0.5 IU/kg (5 dogs), 0.8 IU/kg at a single site (10 dogs), or 0.8 IU/kg at three separate sites (6 dogs). Insulin and glucose concentrations were measured over 24 hours. The shapes of insulin and glucose curves were variable among dogs; and the relationship between insulin dose, concentration, and glucose-lowering effect was nonlinear (Table 2).

Table 2. Pharmacodynamics of three dosing groups

Dose group	Onset of Action	Time to nadir	Duration of Action
0.5 IU/kg at a single site	1 to 14 hours	6 to 16 hours	16 to >24 hours
0.8 IU/kg at a single site	0.5 to 10 hours	5 to >24 hours	16 to >24 hours
0.8 IU/kg divided at three sites	1 to 10 hours	8 to 20 hours	18 to >24 hours

Information for Dog Owners: Please refer to the Client Information Sheet for Dogs for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected dog does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

Effectiveness: A total of 276 client-owned dogs were enrolled in an 84-day field study followed by a 98-day extended-use phase with 276 dogs receiving PROZINC. The dogs included various purebred and mixed breed dogs ranging in age from 2 to 16 years and in weight from 3.3 to 123 pounds. There were 128 neutered males, 8 intact males, 134 spayed females and 6 intact females. Two hundred twenty-four dogs (224) were included in the effectiveness analysis. Dogs were started on PROZINC at a dose of 0.2-0.5 IU/lb (0.5-1.0 IU/kg) once daily. Dogs were evaluated at 7, 14, 21, 28, 42, 63 and 84 days after initiation of therapy. The dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, 21, 28, 42, 63 and 84.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one laboratory variable (blood glucose curve mean, blood glucose curve nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or weight loss). Based on this definition, 162 of 224 cases (72%) were considered successful.

How Supplied: PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

Storage Conditions: Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

Approved by FDA under NADA # 141-297

Marketed by:
Boehringer Ingelheim Animal Health USA Inc. Duluth, GA 30096

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Boehringer Ingelheim

Package Insert for Cats

ProZinc®
(protamine zinc recombinant human insulin)

40 IU/mL

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: PROZINC® is a sterile aqueous protamine zinc suspension of recombinant human insulin.

Each mL contains:

recombinant human insulin	40 International Units (IU)
protamine sulfate	0.466 mg
zinc oxide	0.088 mg
glycerin	16.00 mg
dibasic sodium phosphate, heptahydrate	3.78 mg
phenol (added as preservative)	2.50 mg
hydrochloric acid	1.63 mg
water for injection (maximum)	1005 mg

pH is adjusted with hydrochloric acid and/or sodium hydroxide.

Indication: PROZINC (protamine zinc recombinant human insulin) is indicated for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in cats with diabetes mellitus.

Dosage and Administration: USE OF A SYRINGE OTHER THAN A U-40 SYRINGE WILL RESULT IN INCORRECT DOSING.

FOR SUBCUTANEOUS INJECTION ONLY.

DO NOT SHAKE OR AGITATE THE VIAL.

PROZINC should be mixed by gently rolling the vial prior to withdrawing each dose from the vial. Once mixed, PROZINC suspension has a white, cloudy appearance. Clumps or visible white particles can form in insulin suspensions: do not use the product if clumps or visible white particles persist after gently rolling the vial.

Using a U-40 insulin syringe, the injection should be administered subcutaneously on the back of the neck or on the side of the cat.

Always provide the Client Information Sheet with each prescription.

The initial recommended PROZINC dose is 0.1 – 0.3 IU insulin/pound of body weight (0.2 – 0.7 IU/kg) every 12 hours. The dose should be given concurrently with or right after a meal. The veterinarian should re-evaluate the cat at appropriate intervals and adjust the dose based on both clinical signs and glucose nadirs until adequate glycemic control has been attained. In the effectiveness field study, glycemic control was considered adequate if the glucose nadir from a 9-hour blood glucose curve was between 80 and 150 mg/dL and clinical signs of hyperglycemia such as polyuria, polydipsia, and weight loss were improved.

Further adjustments in the dosage may be necessary with changes in the cat's diet, body weight, or concomitant medication, or if the cat develops concurrent infection, inflammation, neoplasia, or an additional endocrine or other medical disorder.

Contraindications: PROZINC is contraindicated in cats sensitive to protamine zinc recombinant human insulin or any other ingredients in PROZINC. PROZINC is contraindicated during episodes of hypoglycemia.

Warnings: User Safety: For use in cats and dogs only. Keep out of the reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with running water for at least 15 minutes. Accidental injection may cause hypoglycemia. In case of accidental injection, seek medical attention immediately. Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

Animal Safety: Owners should be advised to observe for signs of hypoglycemia (see Client Information Sheet). Use of this product, even at established doses, has been associated with hypoglycemia. A cat with signs of hypoglycemia should be treated immediately. Glucose should be given orally or intravenously as dictated by clinical signs. Insulin should be temporarily withheld and, if indicated, the dosage adjusted.

Any change in insulin should be made cautiously and only under a veterinarian's supervision. Changes in insulin strength, manufacturer, type, species (human, animal) or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Appropriate diagnostic tests should be performed to rule out other endocrinopathies in diabetic cats that are difficult to regulate.

Precautions: Cats presenting with severe ketoacidosis, anorexia, lethargy, and/or vomiting should be stabilized with short-acting insulin and appropriate supportive therapy until their condition is stabilized. As with all insulin products, careful patient monitoring for hypoglycemia and hyperglycemia is essential to attain and maintain adequate glycemic control and to prevent associated complications. Overdose can result in profound hypoglycemia and death.

Glucocorticoids, progestogens, and certain endocrinopathies can have an antagonistic effect on insulin activity. Glucocorticoid and progestogen use should be avoided.

The safety and effectiveness of PROZINC in breeding, pregnant, and lactating cats has not been evaluated.

The safety and effectiveness of PROZINC in kittens has not been evaluated.

Adverse Reactions: Effectiveness Field Study

In a 45-day effectiveness field study, 176 cats received PROZINC. Hypoglycemia (defined as a blood glucose value of < 50 mg/dL) occurred in 71 of the cats at various times throughout the study. Clinical signs of hypoglycemia were generally mild in nature (described as lethargic, sluggish, weak, trembling, uncoordinated, groggy, glassy-eyed or dazed). In 17 cases, the veterinarian provided oral glucose supplementation or food as treatment. Most cases were not associated with clinical signs and received no treatment. One cat had a serious hypoglycemic event associated with stupor, lateral recumbency, hypothermia and seizures.

All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Three cats had injection site reactions which were described as either small, punctate, red lesions; lesions on neck; or palpable subcutaneous thickening. All injection site reactions resolved without cessation of therapy.

Four cats developed diabetic neuropathy during the study as evidenced by plantigrade stance. Three cats entered the study with plantigrade stance, one of which resolved by Day 45. Four cats were diagnosed with diabetic ketoacidosis during the study. Two were euthanized due to poor response to treatment. Five other cats were euthanized during the study, one of which had hypoglycemia. Four cats had received PROZINC for less than a week and were euthanized due to worsening concurrent medical conditions.

The following additional clinical observations or diagnoses were reported in cats during the effectiveness field study: vomiting, lethargy, diarrhea, cystitis/hematuria, upper respiratory infection, dry coat, hair loss, ocular discharge, abnormal vocalization, black stool, and rapid breathing.

Extended Use Field Study

Cats that completed the effectiveness study were enrolled into an extended use field study. In this study, 145 cats received PROZINC for up to an additional 136 days. Adverse reactions were similar to those reported during the 45-day effectiveness study and are listed in order of decreasing frequency: vomiting, hypoglycemia, anorexia/poor appetite, diarrhea, lethargy, cystitis/hematuria, and weakness. Twenty cats had signs consistent with hypoglycemia described as: sluggish, lethargic, unsteady, wobbly, seizures, trembling, or dazed. Most of these were treated by the owner or veterinarian with oral glucose supplementation or food; others received intravenous glucose. One cat had a serious hypoglycemic event associated with seizures and blindness. The cat fully recovered after supportive therapy and finished the study. All cases of hypoglycemia resolved with appropriate therapy and if needed, a dose reduction.

Fourteen cats died or were euthanized during the extended use study. In two cases, continued use of insulin despite anorexia and signs of hypoglycemia contributed to the deaths. In one case, the owner decided not to continue therapy after a presumed episode of hypoglycemia. The rest were due to concurrent medical conditions or worsening of the diabetes mellitus.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim at 1-888-637-4251.

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/reportanimalae.

Information for Cat Owners: Please refer to the Client Information Sheet for Cats for more information about PROZINC. PROZINC, like other insulin products, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the associated clinical signs. Potential adverse reactions include: hypoglycemia, insulin antagonism/resistance, rapid insulin metabolism, insulin-induced hyperglycemia (Somogyi Effect), and local or systemic reactions. The most common adverse reaction observed is hypoglycemia. Signs may include: weakness, depression, behavioral changes, muscle twitching, and anxiety. In severe cases of hypoglycemia, seizures and coma can occur. Hypoglycemia can be fatal if an affected cat does not receive prompt treatment. Appropriate veterinary monitoring of blood glucose, adjustment of insulin dose and regimen as needed, and stabilization of diet and activity help minimize the risk of hypoglycemic episodes. The attending veterinarian should evaluate other adverse reactions on a case-by-case basis to determine if an adjustment in therapy is appropriate, or if alternative therapy should be considered.

Effectiveness: A total of 187 client-owned cats were enrolled in a 45-day field study, with 176 receiving PROZINC. One hundred and fifty-one cats were included in the effectiveness analysis. The patients included various purebred and mixed breed cats ranging in age from 3 to 19 years and in weight from 4.6 to 20.8 pounds. Of the cats included in the effectiveness analysis, 101 were castrated males, 49 were spayed females, and 1 was an intact female.

Cats were started on PROZINC at a dose of 0.1-0.3 IU/lb (0.2-0.7 IU/kg) twice daily. Cats were evaluated at 7, 14, 30, and 45 days after initiation of therapy and the dose was adjusted based on clinical signs and results of 9-hour blood glucose curves on Days 7, 14, and 30.

Effectiveness was based on successful control of diabetes which was defined as improvement in at least one blood glucose variable (glucose curve mean, nadir, or fructosamine) and at least one clinical sign (polyuria, polydipsia, or body weight). Based on this definition, 115 of 151 cases (76.2%) were considered successful. Blood glucose curve means decreased from 415.3 mg/dL on Day 0 to 203.2 mg/dL by Day 45 and the mean blood glucose nadir decreased from 407.9 mg/dL on Day 0 to 142.4 mg/dL on Day 45. Mean fructosamine values decreased from 505.9 µmol/L on Day 0 to 380.7 µmol/L on Day 45.

Cats that completed the effectiveness study were enrolled in an extended use field study. The mean fructosamine value was 342.0 µmol/L after a total of 181 days of PROZINC therapy.

How Supplied: PROZINC is supplied as a sterile injectable suspension in 10 mL and 20 mL multi-dose vials. Each mL of PROZINC contains 40 IU recombinant human insulin.

Storage Conditions: Store in an upright position under refrigeration at 36-46°F (2-8°C). Do not freeze. Protect from light. **Use the 10 mL vial within 60 days of first puncture. Use the 20 mL vial within 80 days of first puncture.**

Approved by FDA under NADA # 141-297

Marketed by:
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

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Boehringer Ingelheim

Drontal® Plus

(praziquantel/pyrantel pamoate/febantel)
Taste Tabs®
Broad Spectrum Chewable Anthelmintic Tablets for Dogs

R.2

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Drontal® Plus Taste Tabs® (praziquantel/pyrantel pamoate/febantel) Broad Spectrum Chewable Anthelmintic Tablets for Dogs are available in three tablet sizes. Each size is scored for convenient oral administration.

Each Drontal Plus Taste Tabs Tablet for Puppies and Small Dogs contains 22.7 mg praziquantel, 22.7 mg pyrantel base as pyrantel pamoate and 113.4 mg febantel.

Each Drontal Plus Taste Tabs Tablet for Medium Sized Dogs contains 68.0 mg praziquantel, 68.0 mg pyrantel base as pyrantel pamoate and 340.2 mg febantel.

Each Drontal Plus Taste Tabs Tablet for Large Dogs contains 136.0 mg praziquantel, 136.0 mg pyrantel base as pyrantel pamoate, and 680.4 mg febantel.

ACTION: Drontal® Plus Taste Tabs® Tablets contain three active ingredients having different modes of action and spectra of activity. Praziquantel is active against cestodes (tapeworms). Praziquantel is absorbed, metabolized in the liver and excreted in the bile. Upon entering the digestive tract from the bile, cestocidal activity is exhibited.[1] Following exposure to praziquantel, the tapeworm loses its ability to resist digestion by the mammalian host. Because of this, whole tapeworms, including the scolices, are very rarely passed after administration of praziquantel. In many instances only disintegrated and partially digested pieces of tapeworms will be seen in the stool. The majority of tapeworms are digested and are not found in the feces.

Pyrantel pamoate is active against hookworms and ascarids. Pyrantel pamoate acts on the cholinergic receptors of the nematode resulting in spastic paralysis. Peristaltic action of the intestinal tract then eliminates the parasite.[2]

Febantel is active against nematode parasites including whipworms. Febantel is rapidly absorbed and metabolized in the animal. Available information suggests that the parasite's energy metabolism is blocked, leading to energy exchange breakdown and inhibited glucose uptake.

Laboratory efficacy and clinical studies conducted with Drontal Plus Anthelmintic Tablets demonstrate that each of the three active ingredients act independently without interference. The combined tablet formulation provides a wide spectrum of activity against the indicated species of intestinal helminths.

INDICATIONS: Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Taste Tabs® Broad Spectrum Chewable Anthelmintic Tablets are indicated for removal of Tapeworms (*Dipylidium caninum, Taenia pisiformis, Echinococcus granulosus,* and removal and control of *Echinococcus multilocularis*) and for removal of Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), Ascarids (*Toxocara canis, Toxascaris leonina*), and Whipworms (*Trichuris vulpis*) in dogs.

CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Dogs treated with elevated levels (6 consecutive days with 3 times the labeled dosage rate) of the combination of febantel and praziquantel in early pregnancy demonstrated an increased incidence of abortion and fetal abnormalities.[8] The effects of Drontal® Plus Anthelmintic Tablets on pregnant animals have not been determined.

There are no known contraindications against the use of praziquantel or pyrantel pamoate in dogs.

PRECAUTIONS: Strict hygienic precautions should be taken when handling dogs or feces suspected of harboring *E. multilocularis*. Infected dogs treated for the first time with Drontal® Plus Taste Tabs® Tablets and dogs treated at intervals greater than 28 days may shed eggs in the feces after treatment. The animal should be held in the clinic during this interval and all feces should be incinerated or autoclaved. If these procedures are not possible, the eggs can be destroyed by soaking the feces in a sodium hypochlorite (bleach) solution of 3.75% or greater.[7] All areas where the animal was maintained or in contact with should be thoroughly cleaned with sodium hypochlorite and allowed to dry completely before reuse.

WARNING: KEEP OUT OF REACH OF CHILDREN.

USE DIRECTIONS

DOSAGE: The presence of parasites should be confirmed by laboratory fecal examination. Weigh the animal before treatment. Administer the proper dosage as specified in the following table as a single oral treatment.

DRONTAL® PLUS TASTE TABS® TABLETS DOSAGE CHARTS

for Puppies and Small Dogs* (2 - 25 lbs.)		for Medium Sized Dogs (26 - 60 lbs.)		for Large Dogs (45 lbs. and greater)	
Body Wt. (lbs.)	No. of Tablets	Body Wt. (lbs.)	No. of Tablets	Body Wt. (lbs.)	No. of Tablets
2 – 4	0.5	26 – 30	1.0	45 – 60	1.0
5 – 7	1.0	31 – 44	1.5	61 – 90	1.5
8 – 12	1.5	45 – 60	2.0	91 – 120	2.0
13 – 18	2.0				
19 – 25	2.5				

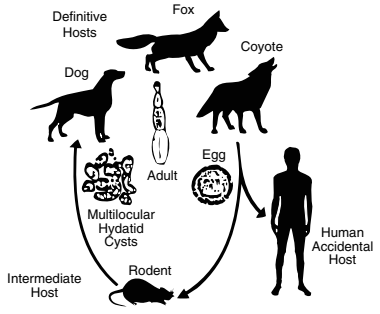
*NOT FOR USE IN PUPPIES LESS THAN 3 WEEKS OF AGE OR DOGS WEIGHING LESS THAN 2 LBS.

ADMINISTRATION: Most dogs find Drontal® Plus Taste Tabs® Tablets palatable. The tablets may be offered to the dog by hand. Alternatively tablets may be given directly by mouth or offered in a small amount of food. Fasting is neither necessary nor recommended prior to or after treatment.

RETREATMENT: For those animals living where reinfections are likely to occur, clients should be instructed in the steps to optimize prevention; otherwise, retreatment may be necessary. This is true in cases of *Dipylidium caninum* where reinfection is almost certain to occur if fleas are not removed from the animal and its environment. In addition, for control of *Echinococcus multilocularis*, a program of regular treatment every 21 to 26 days may be indicated (see *E. multilocularis* section below).

ECHINOCOCCUS MULTILOCULARIS: *Echinococcus multilocularis* is a tapeworm species usually found in wild canids, including foxes, coyotes and wolves. The parasite has also been identified in domestic dogs and cats and is potentially a serious public health concern because it may infect humans.

The life cycle of the parasite is based on a predator-prey relationship as depicted.



The adult tapeworm is small (1-4mm) and resides in the intestinal tract of the definitive host (wild or domestic canids). Eggs from the adult tapeworm are shed in the feces. Rodents such as mice and voles serve as the intermediate host. Eggs ingested by rodents develop in the liver, lungs and other organs to form multilocular cysts. The life cycle is completed after a canid consumes a rodent infected with cysts. Larvae within the cyst develop into adult tapeworms in the intestinal tract of the canid. Eggs may be passed in the feces of the canid approximately 28 days later.

This parasite poses a serious public health problem because of the possibility for human involvement in the life cycle. If eggs shed by an infected canid are accidentally ingested, a highly pathogenic condition (Alveolar Hydatid Disease) results from development of the cyst stage in humans.

The original geographic distribution of *E. multilocularis* was primarily confined to northern areas of North America. Current evidence indicates migration of the parasite well into the continental United States.[3,4]

Domestic dogs living in *E. multilocularis* endemic areas that roam freely with the opportunity to catch wild rodents are at risk of infection. Pet owners should be advised on how to minimize this risk. Proper restraint of dogs should be encouraged, along with regular treatment with Drontal® Plus Taste Tabs® Tablets, following the dosing schedule aforementioned and precautions indicated below.

Additional information on the life cycle and epidemiology of this parasite is available in veterinary parasitology texts.[5,6]

DIAGNOSIS: Diagnosis of *E. multilocularis* in canids is difficult. The adult tapeworm produces no clinical signs of infection. Tapeworm segments (proglottids) are usually not observed in the feces. *E. multilocularis* eggs, observed using microscopic fecal examination procedures, are similar in appearance to those of common species such as *Taenia pisiformis*.

Assistance in the diagnosis of *E. multilocularis* may be available from a state veterinary diagnostic laboratory. Additional information regarding areas where *E. multilocularis* is suspected or has been confirmed may be obtained from area veterinary schools or the Centers for Disease Control in Atlanta, GA.

TREATMENT: Dogs infected with *E. multilocularis* should be treated to prevent exposure of humans to infective eggs and to break the parasite's life cycle.

The dosage of Drontal® Plus Taste Tabs® Tablets for removal of *E. multilocularis* is the same as that indicated for the removal of the other tapeworm species listed on the label. Laboratory efficacy studies conducted with Drontal Plus tablets have demonstrated the recommended dosage is 100% effective.

Under condition of continual exposure to wild rodents, retreatment of the dog at 21-26 day intervals is recommended to prevent the shedding of infectious eggs.

EFFICACY: A total of 176 dogs and puppies with naturally acquired or experimental parasite infections were included in 4 well-controlled laboratory studies to establish the efficacy of Drontal® Plus Anthelmintic Tablets. In addition, 103 dogs and puppies were included in clinical field studies conducted in 5 veterinary clinics at different geographic locations throughout the United States to further evaluate safety and efficacy. These studies included dogs of various sizes, ages and breeds. Data from these studies demonstrated Drontal Plus Anthelmintic Tablets are safe and efficacious for the removal of the parasite species indicated on the label when used as directed.

Results obtained in the laboratory and clinical studies indicate small numbers of hookworm or roundworm eggs may be passed in the feces for up to 7 days after treatment although the worms themselves were eliminated. A follow-up fecal examination should be conducted 2 to 4 weeks after treatment to determine the need for retreatment.

Palatability: Palatability studies with Drontal® Plus Taste Tabs® Tablets were conducted at 3 different veterinary clinics in the United States. These studies included a total of 151 dogs (65 males / 86 females) representing 34 different breeds with body weights ranging from 3.8 – 190 lbs. The tablets were offered free-choice to the dogs by their owners and over 89% of the dogs willingly consumed the tablets.

ADVERSE REACTIONS: None of the 103 dogs treated with Drontal® Plus Anthelmintic Tablets in the clinical field studies exhibited drug-related side effects. Of the 40 dogs treated with Drontal Plus Taste Tabs® Tablets in laboratory studies, two dogs exhibited vomiting, one puppy exhibited bloody/mucoid stool and one puppy exhibited watery/profuse stool.

For customer service or to obtain product information, including Material Safety Data Sheet, call 1-800-633-3796. For medical emergencies or to report adverse reactions, call 1-800-422-9874.

ANIMAL SAFETY: Controlled safety evaluations have been conducted in dogs with Drontal® Plus (praziquantel/pyrantel pamoate/febantel) Anthelmintic Tablets. Dogs receiving up to 5 times the label dosage (35 mg praziquantel, 35 mg pyrantel pamoate and 179 mg febantel per kg of body weight) for 3 consecutive days (3 times the label duration) showed clinical signs of vomition and non-formed stools. One dog receiving a 3 times labeled dose had elevated SGPT, SGOT, CPK and GGT readings (outside of normal range) at 6 days post-treatment. No additional findings were noted in hematology/clinical chemistry parameters nor were there any treatment-related histological lesions. Vomition was the only side effect observed when dogs received a single treatment of 61 mg praziquantel, 61 mg pyrantel pamoate and 305 mg febantel/kg with one dog having an elevated SGPT reading (outside of normal range) at 24 hours post-treatment which had returned to normal by 7 days.

STORAGE CONDITIONS: Drontal® Plus Taste Tabs® Tablets should be stored at or below 77 °F (25 °C).

Un-blistered whole or partial tablets should be stored in a tightly sealed container.

HOW SUPPLIED: Drontal® Plus Taste Tabs® Tablets are available in three tablet sizes:

Code 08758428: 40 tabs/box for Puppies and Small Dogs
Code 08892051: 40 tabs/box for Medium Sized Dogs
Code 08892078: 30 tabs /box for Large Dogs

REFERENCES:

[1] Andrews P. 1976. Pharmacokinetic Studies with DRONCIT® in Animals Using a Biological Assay. Veterinary Medical Review. 2:154-165.

[2] Campbell WC. 1986. The Chemotherapy of Parasitic Infections. J. Parasit. 72(1):45-61.

[3] Hildreth MB Johnson MD and Kazacos KR. 1991. A Zoonosis of Increasing Concern in the United States. Compendium for Cont. Ed. 13(5): 727-740.

[4] Lieby PD Carney WP and Woods CE. 1970. Studies on Sylvatic Echinococcosis, Ill. Host Occurrence and Geographic Distribution of *Echinococcus multilocularis* in the North Central United States. J. Parasit. 56(6): 1141-1150.

[5] Georgi JR and Georgi ME. 1990. Parasitology for Veterinarians. W.B. Saunders Co. 118-138.

[6] Soulsby EJL. 1982. Helminths, Arthropods and Protozoa of Domesticated Animals. 7th Edition. Lea & Febiger. 118-138.

[7] Craig PS and McPharson CNL. 1988. Sodium Hypochlorite as an Ovicide for Echinococcus. Ann Trop Med. and Parasit. 82(2): 211-213.

[8] Freedom of Information Summary (FOI) NADA 133-953 Vercom Paste (febantel and praziquantel).

U.S. Patent No. 7,348,027
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See page 12 for product information summary.

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Proteinuria in Cats

Barry Hedgespeth, BVSc
Karyn Harrell, DVM, DACVIM
North Carolina State University

Following are differential diagnoses for cats presented with proteinuria.

Prerenal

- Hemoglobinuria
- Myoglobinuria
- Light chain immunoglobulins (multiple myeloma, lymphoma)

Renal

- Functional or physiologic
  - Congestive heart failure
  - Strenuous exercise
  - Fever
  - Seizure
  - Exposure to extreme temperatures
- Glomerular
  - Infectious
    - –Bacterial (eg, chronic bacterial infection, mycoplasmal polyarthritis, endocarditis)
    - –Viral (eg, FIV, feline infectious peritonitis, FeLV)
    - –Protozoal (eg, toxoplasmosis)
    - –Fungal (eg, cryptococcosis, other systemic fungal infection)
  - Inflammatory
    - –Acute pancreatitis
    - –Cholangiohepatitis
    - –Chronic progressive polyarthritis
    - –Systemic lupus erythematosus
    - –Other immune-mediated diseases
  - Neoplastic
    - –Leukemia
    - –Lymphoma
    - –Mastocytosis
  - Miscellaneous
    - –Acromegaly
    - –Drug reactions
    - –Diabetes mellitus
    - –Corticosteroids (endogenous/spontaneous hyperadrenocorticism and exogenous)
    - –Hyperthyroidism
    - –Systemic hypertension
  - Familial
    - –Membranous nephropathy
    - –Amyloidosis (Abyssinian, Siamese)
- Tubulointerstitial
  - Chronic kidney disease
  - Acute kidney injury
    - –Toxins (eg, NSAIDs, acetaminophen, ethylene glycol, lilies [*Lilium* and *Hemerocallis* spp], heavy metal ingestion [eg, lead, mercury, arsenic, thallium], insect or snake bite)
    - –Hypotension

Postrenal

- Bacterial cystitis
- Idiopathic cystitis/FLUTD
- Urolithiasis
- Neoplasia (eg, urothelial carcinoma, other)
- Prostatitis (rare in cats)
- Vaginitis
- Pyometra

FLUTD = feline lower urinary tract disease

References

Chew DJ, DiBartola SP, Boyce JT, Gasper PW. Renal amyloidosis in related Abyssinian cats. *J Am Vet Med Assoc*. 1982;181(2):139-142.

Godfrey DR, Day MJ. Generalised amyloidosis in two Siamese cats: spontaneous liver haemorrhage and chronic renal failure. *J Small Anim Pract*. 1998;39(9):442-447.

Harley L, Langston C. Proteinuria in dogs and cats. *Can Vet J*. 2012;53(6):631-638.

Littman MP. Protein-losing nephropathy in small animals. *Vet Clin North Am Small Anim Pract*. 2011;41(1):31-62.

Vaden SL. Glomerular Diseases. In: Ettinger SJ, Feldman EC, Côté E, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. Elsevier; 2017:1959-1972.

Vaden SL, Elliot J. Management of proteinuria in dogs and cats with chronic kidney disease. *Vet Clin North Am Small Anim Pract*. 2016;46(6):1115-1130.

Wright NG, Nash AS, Thompson H, Fisher EW. Membranous nephropathy in the cat and dog: a renal biopsy and follow-up study of sixteen cases. *Lab Invest*. 1981;45(3):269-277.

TREATING DIARRHEA: THINK BEYOND ANTIMICROBIALS

By Donna Raditic, DVM, DACVN, CVA and Laura Gaylord, DVM, DACVN

Diarrhea is a common problem in general practice and can be chronic or recurrent in some patients. Numerous diagnostic tests are often performed along with empirical treatments that include the use of dietary interventions, parasiticides, and antimicrobials. There is increasing concern about the risks of indiscriminate use of antimicrobials as antibiotic resistance has become a global issue facing both human and veterinary medicine. Antibiotic resistance is a growing medical problem due to persistent, selective pressure from the widespread use of antimicrobials in humans, animals, and agriculture.[1,2] Indiscriminate use of antimicrobials in the veterinary diarrhea patient may also have detrimental consequences creating antimicrobial resistance as a result of individual, long-term disruptions of normal bacterial populations and worsening of gastrointestinal signs.[2,3]

Instead of using antimicrobials for patients with diarrhea, veterinarians should use dietary intervention and consider the use of probiotics, prebiotics, and other gastrointestinal support supplements.[3-5] Probiotics are defined as live microorganisms, which when consumed in adequate amounts as part of a food, may confer a health benefit on the host (Food and Agriculture Organization of the United Nations/World Health Organization, 2002). Those studied in pet health belong to the genera of Lactobacillus *(L. acidophilus, L. casei, L. plantarum, L. paracasei, L. lactis, L. rhamnosus)*, Bifidobacterium *(B. infantis, B. lactis, B. longum and B. bifidum)* and Enterococcus *(E. faecium)*. These probiotics have been shown to stimulate growth of resident healthy bacteria, to alter bacterial imbalance directly or indirectly via interactions with enterocytes and the gut immune system.[6] Less familiar organisms found in probiotics include the spore-forming bacterium Bacillus *(B. coagulans, B. subtilis)* and yeasts *(Saccharomyces cerevisiae, Saccharomyces boulardii)* and fungi *(Aspergillus oryzae)*.[1,7-18] Saccharomyces studies in dogs and other species suggest it may improve fecal characteristics and support a healthy gut immune system.[11,19-21]

Instead of using antimicrobials for patients with diarrhea, veterinarians should use dietary intervention and consider the use of probiotics, prebiotics, and other gastrointestinal support supplements.[3-5]

Prebiotics are defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" and are used in both veterinary therapeutic diets and supplements intended to support gastrointestinal health.[1] Studies of complex carbohydrates or fibers such as fructooligosaccharides (FOS) and mannan-oligosaccharide (MOS), and β glucan have shown some benefit and impact on the gut microbiome composition. Prebiotics can alter gut motility and/or may be fermented to produce short chain fatty acids, especially butyrate which is a source of fuel for enterocytes.[1,3-6,10,22,23] Other nutrients such as essential B vitamins, electrolytes (sodium, potassium, chloride) and L-glutamine can be found in pet supplements that support proper digestion and normal gastrointestinal function. The amino acid, L-glutamine is utilized by enterocytes as an intermediary in energy metabolism, promoting enterocyte proliferation, regulating tight junction proteins, suppressing proinflammatory signaling and protecting against cellular stress during normal and pathological conditions. The gut uses about 30% of body glutamine and although classically considered a non-essential amino acid, L-glutamine is considered "conditionally essential" during certain catabolic states, such as trauma or sepsis.[24-29]

Various botanicals such as slippery elm *(Ulmus rubra)*, licorice *(Glycyrrhiza glabra)*, aloe *(Aloe vera)*, ginger *(Zingiber officinale)*, and psyllium *(Plantago ovata)* may also be found as ingredients in gastrointestinal pet supplements. Used historically for gastrointestinal health in the medicine systems of other cultures, studies of the benefits of these botanicals are scant, but they may have prebiotic effect and/or antioxidant properties.[30-38]

As there are increasing concerns of the overuse of antimicrobials to treat veterinary patients with diarrhea there is a need for more research and consideration of other treatments such as probiotics, prebiotics, gut specific nutrients, and botanicals individually or in specific combinations.

For a full list of references, visit:
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Lactobacillus bulgaricus
Lactobacillus reuteri

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Vitamin B5 (Pantothenic Acid)	**10.5 mg**
Vitamin B6 (Pyridoxine HCl)	**2.5 mg**
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FAQs ABOUT HEARTWORM DIAGNOSIS, PREVENTION AND MANAGEMENT

Q **Dear AHS,**
A local shelter treats heartworm-positive patients with a protocol consisting of a month of doxycycline immediately followed by two consecutive melarsomine injections that are administered during one two-day stay. We typically see patients several months after they've been adopted. How should these patients be managed at this point? *-Dr. H.*

ANGELE BICE, DVM
OWNER,
SUMMERVILLE PET CLINIC
SUMMERVILLE, SOUTH CAROLINA

THE SHORT ANSWER

While a 2-dose adulticide protocol only reduces the worm burden by 90% vs. the 98% achieved with a 3-dose protocol, there are alternatives to giving additional doses of melarsomine to this dog at this time.

A In my practice, I've worked with shelters that follow similar protocols vs. the 3-injection regimen recommended by the American Heartworm Society (AHS). Unfortunately, many shelters have limitations posed by cost and time constraints and, thus, opt for protocols that fit their budget and staffing capabilities. While the protocol you describe is not uncommon, it does leave the adopter and their veterinarian with questions.

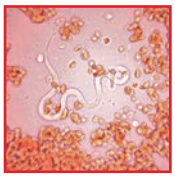
Should you test the dog? You might be tempted to retest the patient at this point, but I would counsel you to wait. The AHS recommends retesting nine months after the last injection of melarsomine because the results from earlier testing are likely to be unreliable. Antigen tests are most sensitive in detecting gravid female worms, but doxycycline weakens the ability of heartworms to reproduce. Conversely, it is possible that 100% of the adult worms might be dead, but the test would detect antigen in the tissue of the dead worms.

Unless it was performed at the shelter, one test you *should* administer is a microfilaria (MF) test, because melarsomine is unlikely to kill microfilaria if they are still present. If the test is positive, a microfilaricide such as topical moxidectin should be administered.

Is additional treatment needed? By giving just two injections 24 hours apart, you can expect a 90% reduction in heartworm burden vs. the 98% reduction achieved with the three-injection AHS treatment protocol. That sounds like a small difference in efficacy until you remember that reducing worm burden and eliminating all adult heartworms are two different things.

The question: should you be satisfied with a 90% reduction in adult worms, especially if the dog is on a monthly preventive? Or should you consider giving another two doses of melarsomine 24 hours apart to complete the treatment protocol? Both are viable options. However, because the remaining worms should be greatly weakened at this point, my recommendation would be to administer a heartworm preventive with known activity against adult worms to target any remaining worms. The dog should then be tested 9 months after the last melarsomine injection with an immune complex dissociation antigen test. There is no need to repeat doxycycline therapy as long as the dog has been on uninterrupted heartworm prevention since treatment began.

Next Steps to Consider:



• Test for MF and treat if needed

• Target remaining adult worms

• Re-test dog 9 months after last melarsomine injection

• Maintain dog on year-round HW prevention

CONSULT THE EXPERT

COMMON TIBIAL PLATEAU-LEVELING OSTEOTOMY COMPLICATIONS

Dominique Hemmings, DVM
Tuskegee University

Selena Tinga, DVM, PhD, DACVS-SA
The Ohio State University

The cranial cruciate ligament (CrCL) resists cranial tibial translation, internal tibial rotation, and stifle hyperextension.[1] Rupture of the CrCL (CrCLR) is the most common cause of hindlimb lameness in dogs,[1] often resulting in instability, meniscal tearing, and osteoarthritis. CrCL degeneration is caused by a combination of factors, including age, obesity, trauma, genetics, and abnormal bony morphology.[1]

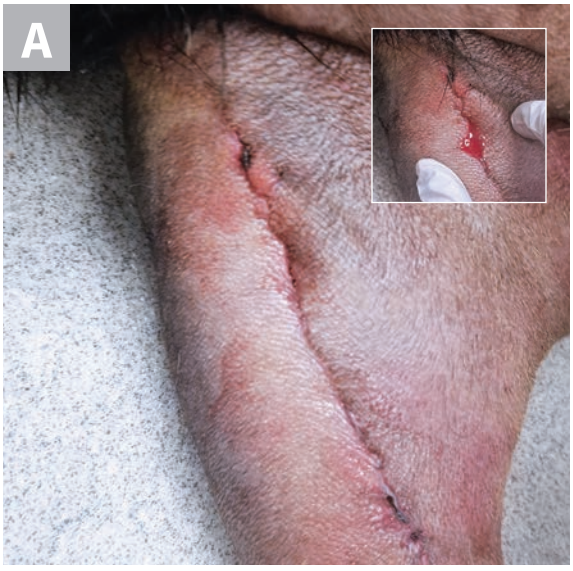
Complete CrCLR can typically be diagnosed via palpation (positive cranial drawer or tibial thrust), although early or partial tears are more challenging to diagnose.[1] Radiography should be performed to identify findings supportive of CrCLR (eg, stifle joint effusion, osteoarthritis, cranial tibial subluxation), to rule out other causes of pain or instability (eg, fractures, neoplasia), and for surgical planning.[1]

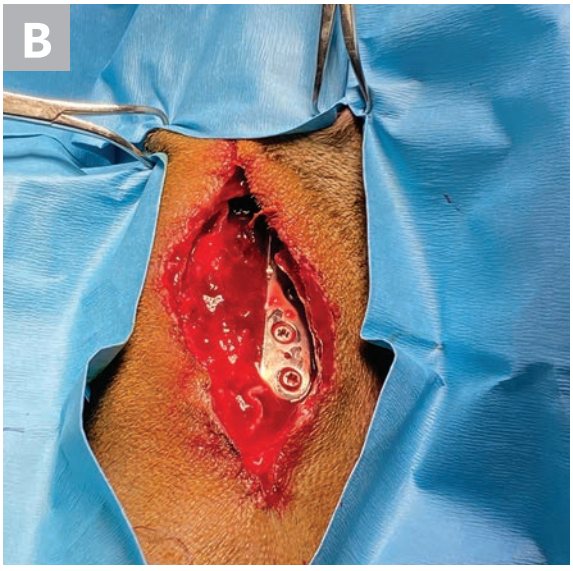
Treatment options for CrCLR include osteotomy-based procedures, extracapsular suture procedures, and nonsurgical management. A survey suggested that surgeons prefer tibial plateau-leveling osteotomy (TPLO) for treatment of most cases of CrCLR in dogs weighing >33 lb (15 kg).[2-7] Several studies report an equal to superior outcome for TPLO as compared with extracapsular suture procedures and other osteotomy procedures.[3-7] For example, some studies have shown TPLO to have a quicker return to normal weight bearing, higher pet owner satisfaction, and slower progression of osteoarthritis.[3-7] However, 10% to 34% of dogs treated with TPLO develop a complication, with up to 4% requiring revision surgery.[7] Complications may arise from inappropriate candidate selection, imperfect surgical technique, or poor owner compliance, but complications are also an inherent risk of surgery in any patient.

Common TPLO Complications

Surgical Site Infection

The incidence of surgical site infection (SSI) after TPLO ranges from 1.3% to 25.6%, with a wide reported range secondary to variable definitions of SSI risk factors and methodology.[8-12] SSI can occur in superficial and/or deep tissues and





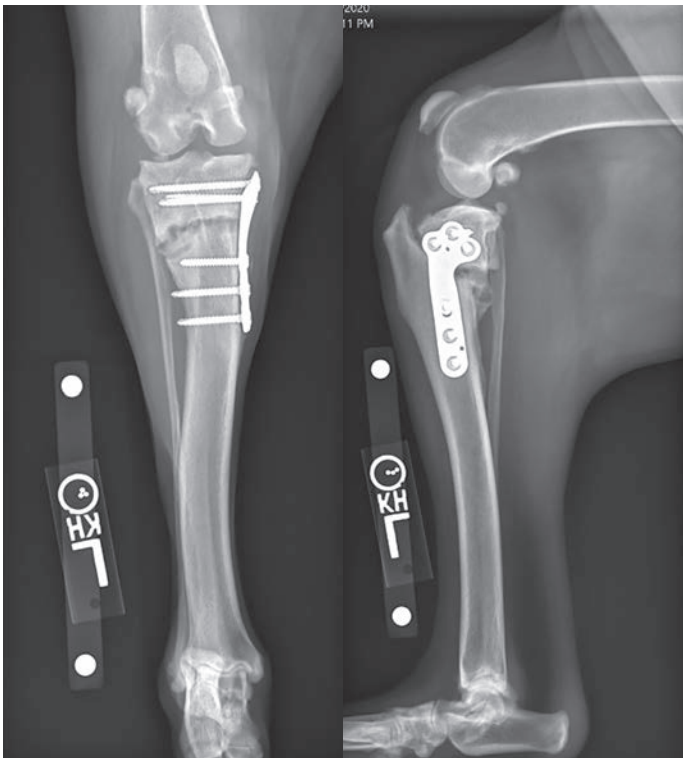
▲ **FIGURE 1** A 5-year-old neutered male Rottweiler that developed a deep surgical site infection 5 days after TPLO. Prior to removal of intradermal sutures (***A***), thick serosanguinous discharge was easily expelled from the incision in multiple locations (***inset***). After removal of intradermal sutures (***B***), the TPLO plate was immediately visible, indicating dehiscence of the fascial closure, and the tissues appeared inflamed and were coated with a thick mucoid film. The wound was managed as an open wound for 4 days then closed once tissues appeared healthy, and the implant was not removed; the patient remained on oral culture-based antibiotics until healing of the osteotomy (delayed union). This dog did not develop osteomyelitis and had no lameness at the last follow-up.

includes the subcategories of soft tissue infection, implant-associated infection, osteomyelitis, or septic arthritis. A large review reported the incidence of SSI subcategories occurring after TPLO by taking case numbers from numerous primary studies; wound complications occurred in 7.8% of TPLO cases, implant-associated infection occurred in 3.4%, osteomyelitis occurred in 0.6%, and septic arthritis occurred in 0.8%.[6]

Reported risk factors for development of post-TPLO SSI include German shepherd breed, heavier body weight, undergoing a meniscectomy, inexperienced surgeon, prolonged duration of surgery and anesthesia.[8-10] One study reported a nonsignificant trend toward increased SSI rate after TPLO in dogs with dermatitis[8]; thus, the authors recommend giving consideration to surgical delay and controlling dermatitis prior to elective orthopedic surgery, particularly when dermatitis is severe or within the surgical site. In addition to sterile technique, the risk for SSI is likely mitigated by meticulous tissue handling, accurate wound closure, minimizing the duration of surgery and anesthesia, copious lavage, and perioperative administration of a first-generation cephalosporin antibiotic (eg, cefazolin).[8,9] One study documented a significant reduction in SSI rate from 8.5% to 1.3% after implementation of a strict infection control protocol that included use of an adhesive iodine-impregnated drape during surgery, single use gloves at all times when handling dogs, and an Elizabethan collar, in addition to multiple additional efforts.[11]

The use of perioperative antibiotics is supported, but there is conflicting evidence regarding the use of postoperative antibiotics, and the potential protective effects must be weighed against the risk for developing bacterial drug resistance.[8-10] If an SSI occurs, immediate and aggressive wound management, bacterial culture, and antibiotic therapy are all recommended to control the infection while the bone heals. Even superficial soft tissue infections can progress to implant-associated infections and osteomyelitis, especially if not treated appropriately, and can result in delayed union, nonunion, or persistent infection (***Figures 1*** and ***2***).[7] Treatment for an implant-associated infection, osteomyelitis, or septic arthritis requires long-term antibiotic therapy, possible surgical flush, debridement, and/or local antimicrobial therapies, as well as implant removal in many cases, once bone healing is confirmed.[13]

Continued ▶



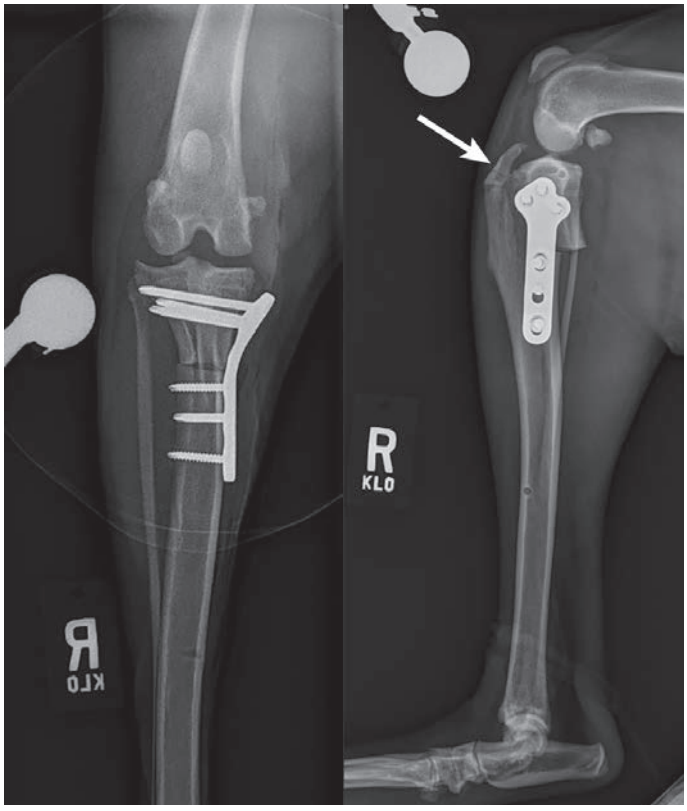
▲ **FIGURE 2** Radiographs from an 8-year-old spayed Rottweiler that underwent TPLO and was diagnosed with a superficial SSI 2 weeks postoperatively at another hospital. The SSI was treated with a 10-day course of antibiotics. The dog was presented to The Ohio State University Veterinary Hospital 6 weeks after surgery for recurrent lameness; the incision was healed, but osteomyelitis was confirmed on radiographs and fine-needle aspirate and cytology. Culture-based antibiotics were prescribed, but the infection did not resolve, the lameness was persistent, and the osteotomy became a nonunion. The patient was euthanized after developing a T3-L3 myelopathy suspected to be related to systemic infection.

CrCL = cranial cruciate ligament
CrCLR = cranial cruciate ligament rupture
SSI = surgical site infection
TPLO = tibial plateau-leveling osteotomy

In rare cases, infection cannot be controlled, bone healing cannot be achieved, and amputation or euthanasia is required.

Residual Instability

Cranial-caudal stifle instability is present postoperatively in one-third of TPLO-treated patients.[14] Though the majority of dogs with postoperative instability are nonclinical, even nonclinical residual instability may result in a reduced long-term outcome. A more severe instability known as *pivot shift*, which involves cranial tibial subluxation coupled with a sudden lateral motion of the stifle during weight bearing, occurs in up to 3% of cases.[7,12] The cause of residual instability has been hypothesized to be related to meniscectomy (or meniscal release) or incomplete plateau leveling.[12,14] Incorrect osteotomy position (eg, osteotomy is positioned distally; ***Figure 3***) or plateau rock-back can affect success in achieving or maintaining plateau leveling and therefore may affect stifle stability.[1] In some cases, stifle instability after TPLO (including pivot shift) may resolve with time,[8] likely due to improved muscular strength, which may support the hypothesis that some degree of instability can occur due to muscle weakness and further support the recommendation for postoperative physical therapy.



▲ **FIGURE 3** Immediate postoperative radiographs from a 2-year-old spayed medium-size crossbreed dog showing an inappropriately distally positioned TPLO. Distalizing the TPLO reduces the leveling achieved with planned rotation, leaves a narrow tibial crest (***arrow***), and positions the osteotomy in diaphyseal bone (slower to heal than metaphyseal bone). Also notable is the cranial position of the distal jig pin hole, which may predispose the patient to tibial diaphyseal fracture. This osteotomy position can be compared with that shown in ***Figure 4***, in which the osteotomy position and resultant crest shape are appropriate.

Medial Meniscal Tears

Meniscal pathology causes lameness and progression of osteoarthritis; therefore, intra-articular examination at the time of TPLO is necessary for the diagnosis and treatment of concurrent meniscal pathology. In the months following TPLO, postoperative meniscal tears are diagnosed in 1.8% to 10.5% of cases in which the meniscus was classified as normal and left untreated at the time of TPLO.[6,15,16] Some of these cases likely represent meniscal tears that were present but not identified at the time of original surgery. The sensitivity of detecting meniscal tears can be increased by using arthroscopy (vs arthrotomy) and by using a stifle distractor and meniscal probe during joint examination.[1,16,17] Development of a postoperative meniscal tear is likely related to the presence of residual stifle joint instability and often results in persistent lameness, requiring an additional procedure for meniscal debridement.

Patellar Tendinosis

Patellar tendon thickening (***Figure 4***) is a benign process that occurs in 80% to 100% of dogs after TPLO.[18] In up to 7% of cases, this thickening is associated with pain and lameness (patellar tendinosis).[18] Patellar tendinosis usually responds to NSAIDs and rest, followed by gradual return to activity,[18] with anecdotal evidence also supporting the use of shockwave therapy and physical rehabilitation therapy.

Intra-Articular Screw Placement

Intra-articular screw placement likely leads to persistent pain and hastened osteoarthritis development if not addressed immediately. The incidence of intra-articular screw placement during TPLO ranges from <0.1% to 7.1%.[6,12,19,20] In one study comparing the use of locking and nonlocking TPLO plates, nonlocking TPLO plates were associated with an increased risk for intra-articular screw placement; this is likely because locking TPLO plates are typically precontoured with a screw trajectory designed to minimize the risk of intra-articular or intra-osteotomy screw placement.[20] However, poor plate positioning, intraoperative plate contouring, or cross-threading can affect screw trajectory and result in intra-articular screw placement when using locking plates (***Figure 5***, next page).[20] Postoperative radiographs must be scrutinized for intra-articular screws, and offending screws must be immediately redirected or shortened to prevent the long-term effects of this complication.

Uncommon Complications

The following complications are uncommon but can be catastrophic and therefore warrant individual discussion. Poor surgical technique will increase the incidence of these complications.

Plateau Rock-Back

Rock-back (ie, loss of plateau leveling) results from failure—sometimes catastrophic—of the plate, screws, and/or plateau segment. Some studies report more loss of osteotomy reduction in the postoperative period when nonlocking constructs are used as compared with locking constructs.[21] Rock-back can affect long-term outcome if it results in recurrent stifle instability. Implant or bone failure can occur with use of either nonlocking or locking constructs in cases of poor surgical technique (eg, poor osteotomy position, incomplete osteotomy compression, improper plate/screw position or application) or incomplete postoperative activity restriction and can have catastrophic consequences.

Tibial Tuberosity Fracture

The risk for tibial tuberosity fracture may be increased by an osteotomy position that results in a narrow crest (***Figure 3***), by bilateral simultaneous TPLO procedures, or by other factors that either decrease the strength of the patellar tendon's anchor point or increase the pull of the patellar tendon.[7,22] Many cases do not require intervention, although surgical stabilization may be required if the fragment is unstable.

Fibular Fracture

Inadvertent drilling of the fibula during TPLO increases the risk for fibular fracture 10-fold.

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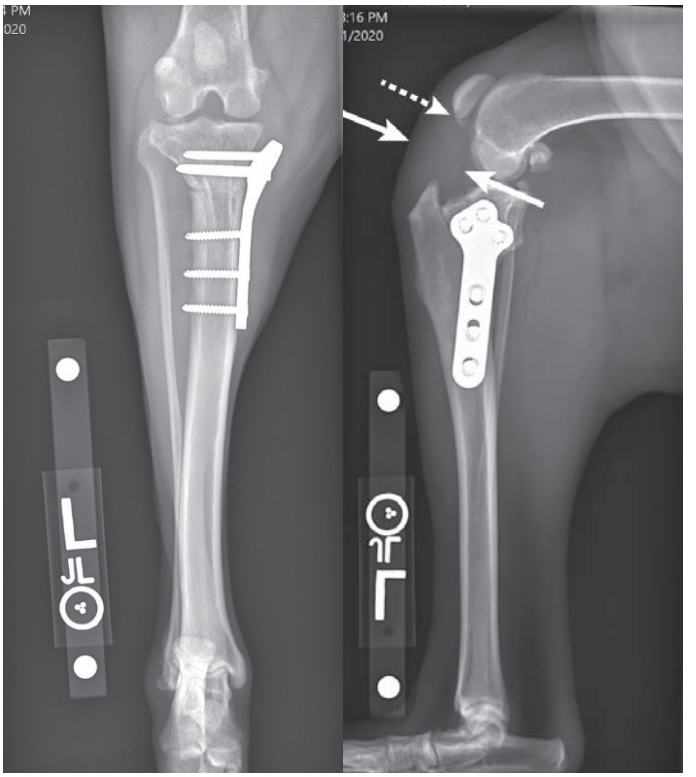


▲ **FIGURE 4** Radiographs from a 7-year-old spayed golden retriever presented with recurrent lameness 3 months after TPLO. A moderate weight-bearing lameness and pain on palpation of the cranial stifle/patellar tendon was identified on examination of the operated limb. Radiographs revealed thickening of the patellar tendon (***solid arrows***) and an apical patellar fracture (***dashed arrow***). Lameness resolved with rest, NSAID therapy, and shockwave therapy.

TPLO = tibial plateau-leveling osteotomy

Although it is suspected that the risk for fracture is higher when the fibular drill hole is left unfilled—and therefore it is recommended to fill the hole—this was not proven statistically (likely a type II statistical error).[23] Increased body weight is also a risk factor for fibular fracture after TPLO.[23] Fibular fracture eliminates the fibula's splinting function, which likely aids in stabilizing the osteotomy and, therefore, fibular fractures may increase the incidence and degree of rock-back.[23]

Patellar Luxation

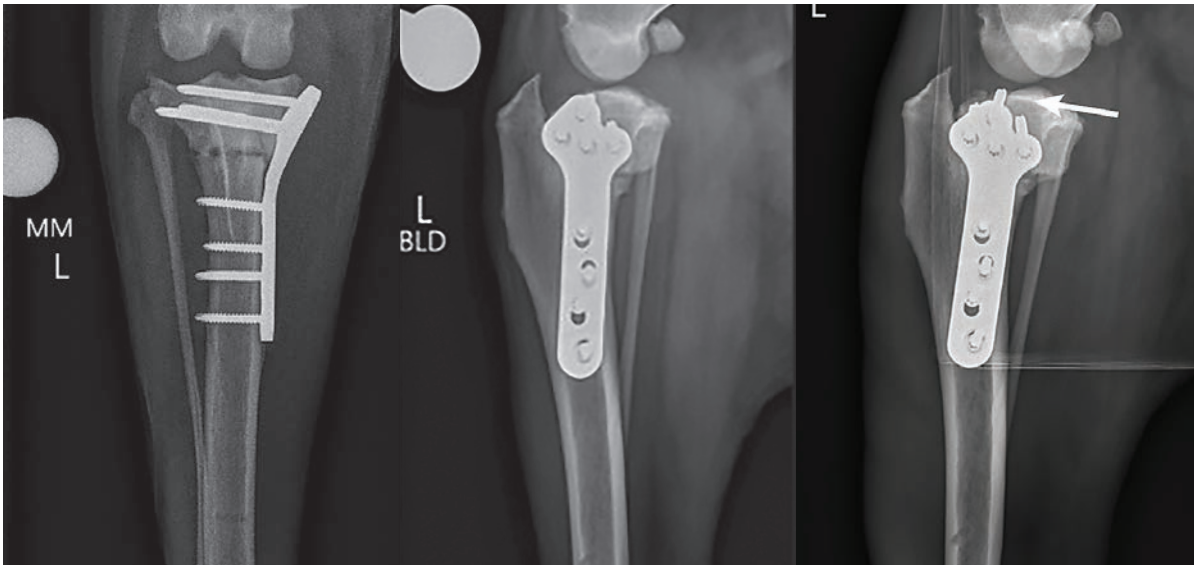
Patellar luxation occurs in <1% of cases following TPLO, although in one study, the majority of postoperative patellar luxations required revision surgery.[7,15] The theorized causes of patellar luxation as a complication of TPLO include muscle atrophy, closure of the medial retinaculum under too much or too little tension, severe joint effusion after surgery, and creation of tibial malalignment.[15]

Other Complications

Additional complications to consider include anesthetic complications, minor incisional complications (eg, minor dehiscence, seroma, suture reaction), intraoperative hemorrhage (arterial), delayed/nonunion, implant failure, tibial diaphyseal fracture, creation of angular deformity, collateral ligament or patellar tendon trauma, and implant-associated sarcomas.[7,15,24]

Conclusion

Preventing complications during recovery depends on both preoperative and intraoperative decision making, along with owner education and compliance. Owners must be instructed to keep Elizabethan collars on their pet until the incision is healed. For ≈8 weeks following surgery, or until radiographic healing is demonstrated, patient activity should be strictly controlled; no concussive activity or free roaming should be allowed, but gradually increasing duration of leashed walking and other controlled strengthening exercises is important to promote muscular recovery and bone healing. Adhering to these strict guidelines should mitigate the risk for incisional complications, implant and bone failure, and delayed healing.



▲ **FIGURE 5** Radiographs from a 5-year-old neutered male Bernese mountain dog with persistent lameness 2 months following TPLO. Radiographs revealed the proximal-most screw violating the joint space (***arrow***). This is best visualized on the third (oblique) view and was not identified on immediate postoperative radiographs. The locking plate is designed to reduce the risk of intra-articular screw placement, but this plate was contoured intraoperatively to accommodate for excessive medial buttress, which resulted in a screw trajectory directed toward the joint space.

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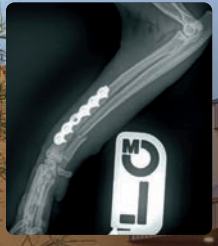

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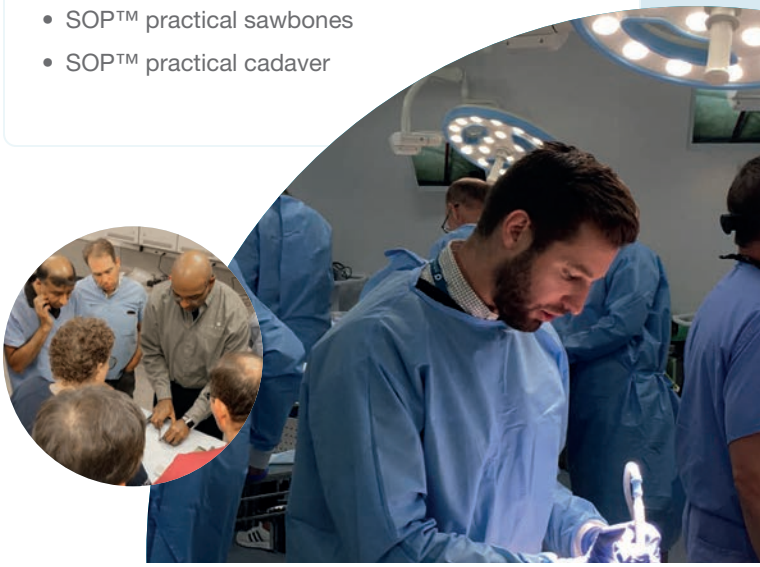
- SOP™ biomechanics
- SOP™ clinical recommendations
- SOP™ practical sawbones
- SOP™ practical cadaver



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References

1. Kowaleski M, Boudrieau R, Pozzi A. Stifle Joint. In: Johnston S, Tobias K, Peck J, Kent M, eds. *Veterinary Surgery: Small Animal*. Vol 1. 2nd ed. Elsevier; 2018:1071-1168.
2. von Pfeil DJ, Kowaleski MP, Glassman M, Dejardin LM. Results of a survey of Veterinary Orthopedic Society members on the preferred method for treating cranial cruciate ligament rupture in dogs weighing more than 15 kilograms (33 pounds). *J Am Vet Med Assoc*. 2018;253(5):586-597.
3. Krotscheck U, Nelson S, Todhunter R, Stone M, Zhang Z. Long term functional outcome of tibial tuberosity advancement vs. tibial plateau leveling osteotomy and extracapsular repair in a heterogenous population of dogs. *Vet Surg*. 2016;45.
4. Gordon-Evans W, Griffon D, Bubb C, Knap K, Sullivan M, Evans R. Comparison of lateral fabellar suture and tibial plateau leveling osteotomy techniques for treatment of dogs with cranial cruciate ligament disease. *J Am Vet Med Assoc*. 2013;243:675-680.
5. Lazar T, Berry C, Dehaan J, Peck J, Correa M. Long-term radiographic comparison of tibial plateau leveling osteotomy versus extracapsular stabilization for cranial cruciate ligament rutpre. *Vet Surg*. 2005;34:133-141.
6. Beer P, Bockstahler B, Schnabl-Feichter E. Tibial plateau leveling osteotomy and tibial tuberosity advancement - a systematic review. *Tierarztl Prax Ausg K Kleintiere Heimtiere*. 2018;46(4):223-235.
7. Bergh M, Sullivan C, Ferrel C, Troy J, Budsberg S. Systematic review of surgical treatments for cranial cruciate ligament disease in dogs. *J Am Anim Hosp Assoc*. 2014;50:315-321.
8. Lopez DJ, VanDeventer GM, Krotscheck U, et al. Retrospective study of factors associated with surgical site infection in dogs following tibial plateau leveling osteotomy. *J Am Vet Med Assoc*. 2018;253(3):315-321.
9. Hagen CR, Singh A, Weese JS, Marshall Q, zur Linden A, Gibson TW. Contributing factors to surgical site infection after tibial plateau leveling osteotomy: A follow up retrospective study. *Vet Surg*. 2020;49:930-939.
10. Clark AC, Greco JJ, Bergman PJ. Influence of administration of antimicrobial medications after tibial plateau leveling osteotomy on surgical site infections: A retrospective study of 308 dogs. *Vet Surg*. 2019;49:106-113.
11. Stine SL, Odum SM, Mertens WD. Protocol changes to reduce implant-associated infection rate after tibial plateau leveling osteotomy: 703 dogs, 811 TPLO (2016-2014). *Vet Surg*. 2018;47:481-489.
12. Gatineau M, Dupuis J, Plante J, Moreau M. Retrospective study of 476 tibial plateau levelling osteotomy procedures: Rate of subsequent 'pivot shift', meniscal tear and other complications. *Vet Comp Orthop Traumatol*. 2011;24:333-341.
13. Marchevsky A, Read R. Bacterial septic arthritis in 19 dogs. *Aust Vet J*. 1999;77:233-237.
14. Tinga S, Kim SE, Banks SA, et al. Femorotibial kinematics in dogs treated with tibial plateau leveling osteotomy for cranial cruciate ligament insufficiency: An in-vivo fluoroscopic analysis during walking. *Vet Surg*. 2020;49(1):187-199.
15. Coletti TJ, Anderson M, Grose MJ, Madsen R. Complications associated with tibial plateau leveling osteotomy: A retrospective of 1519 procedures. *Can Vet J*. 2014;55:249-254.
16. Thieman K, Tomlinson J, Fox D, Cook C, Cook J. Effect of meniscal release on rate of subsequent meniscal tears and owner-assessed outcome in dogs with cruciate disease treated with tibial plateau leveling osteotomy. *Vet Surg*. 2006;35:705-710.
17. Pozzi A, Hildreth III B, Rajala-Schultz P. Comparison of arthroscopy and arthrotomy for diagnosis of medial meniscal pathology: An ex vivo study. *Vet Surg*. 2008;37:749-755.
18. Carey K, Aiken S, DiResta G, Herr L, Monette S. Radiographic and clinical changes of the patellar tendon after tibial plateau leveling osteotomy: 94 cases (2001-2003). *Vet Comp Orthop Traumatol*. 2005;18:235-242.
19. Pacchiana PD, Morris E, Gillings SL, Jessen CR, Lipowitz AJ. Surgical and postoperative complications associated with tibial plateau leveling osteotomy in dogs with cranial cruciate ligament rupture: 397 cases (1998-2001). *J Am Vet Med Assoc*. 2003;222(2):184-193.
20. Krotscheck U, Thompson M, Ryan K, Mohammed H. Comparison of TPA, bone healing, and intra-articular screw placement using conventional nonlocked application of surgeon-contoured versus locked application of precontoured TPLO plates in dogs. *Vet Surg*. 2012;41:931-937.
21. Conkling A, Fagin B, Daye R. Comparison of tibial plateau angle changes after tibial plateau leveling osteotomy with conventional or locking screw technology. *Vet Surg*. 2010;39:475-481.
22. Bergh M, Rajala-Schultz P, Johnson K. Risk factors for tibial tuberosity fracture after tibial plateau leveling osteotomy in dogs. *Vet Surg*. 2008;37:374-382.
23. Taylor J, Langenbach A, Marcellin-Little DJ. Risk factors for fibular fracture after TPLO. *Vet Surg*. 2011;40(6):687-693.
24. Selmic L, Ryan S, Boston S, et al. Osteosarcoma following tibial plateau leveling osteotomy in dogs: 29 cases (1997-2011). *J Am Vet Med Assoc*. 2014;244(9):1053-1059.

TPLO = tibial plateau-leveling osteotomy

LEPTOSPIROSIS

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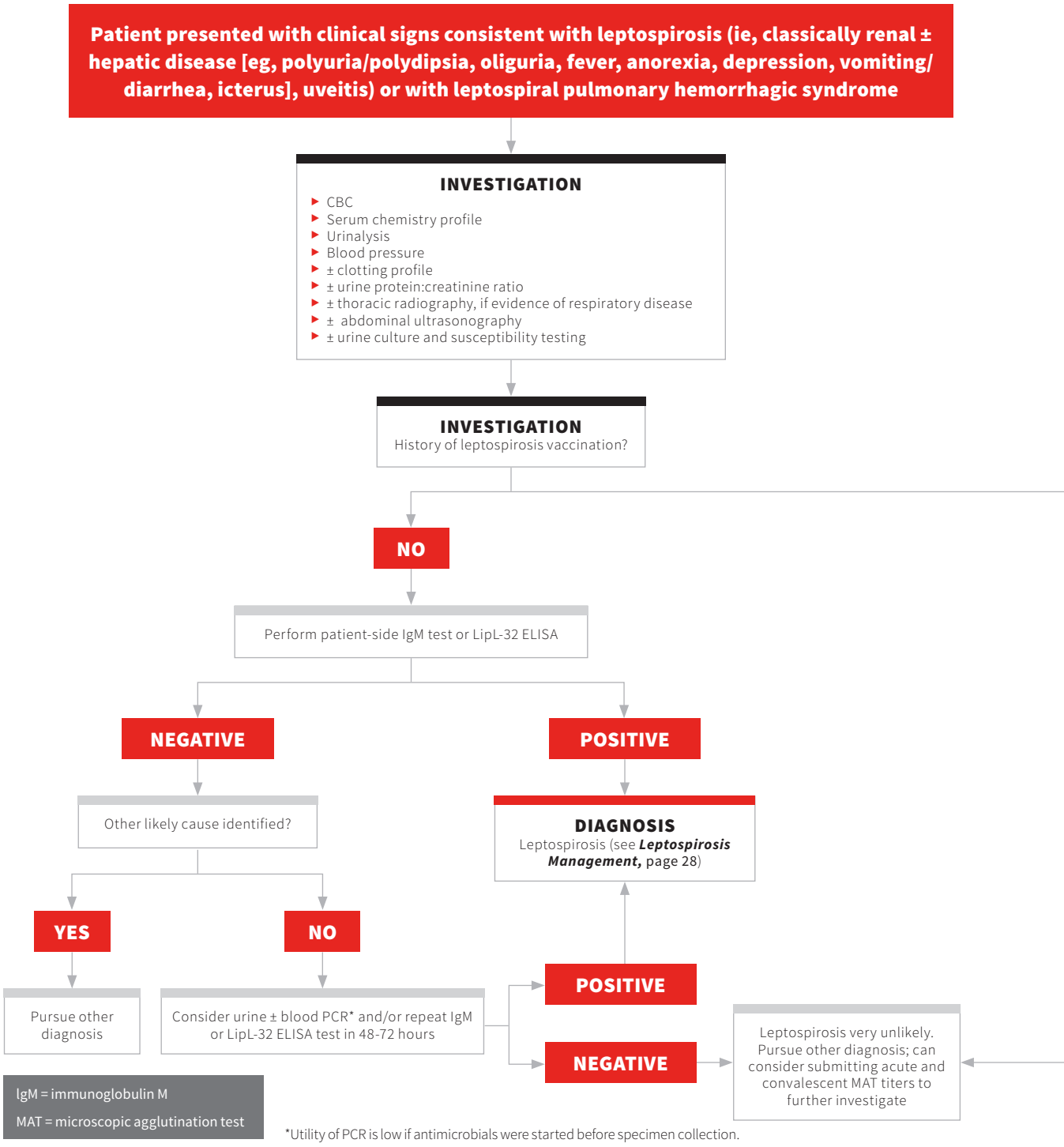
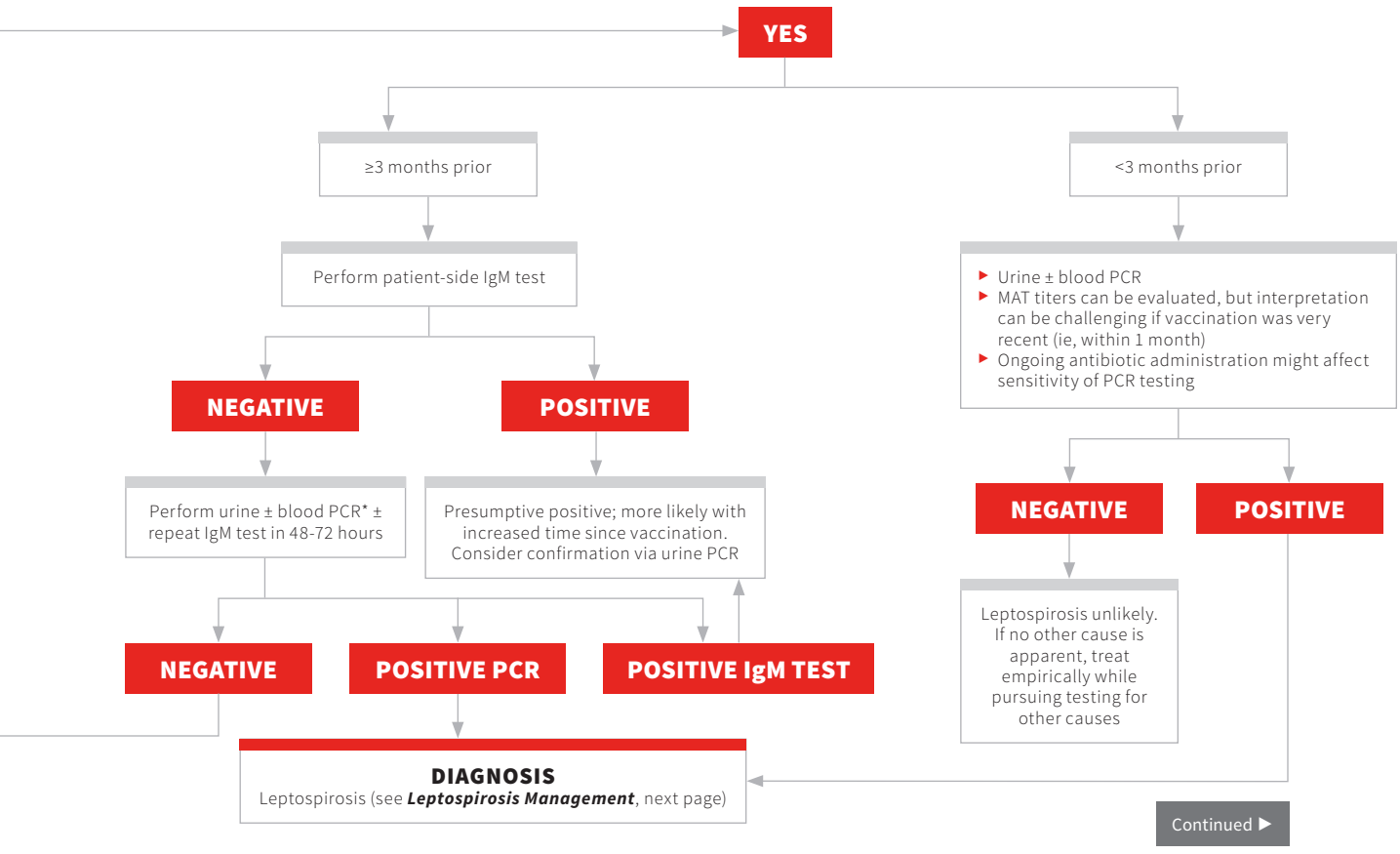
Ontario, Canada




YES
≥3 months prior
<3 months prior
Perform patient-side IgM test
▸ Urine ± blood PCR
▸ MAT titers can be evaluated, but interpretation can be challenging if vaccination was very recent (ie, within 1 month)
▸ Ongoing antibiotic administration might affect sensitivity of PCR testing
NEGATIVE
POSITIVE
Perform urine ± blood PCR* ± repeat IgM test in 48-72 hours
Presumptive positive; more likely with increased time since vaccination. Consider confirmation via urine PCR
NEGATIVE
POSITIVE
NEGATIVE
POSITIVE PCR
POSITIVE IgM TEST
Leptospirosis unlikely. If no other cause is apparent, treat empirically while pursuing testing for other causes
DIAGNOSIS
Leptospirosis (see ***Leptospirosis Management***, next page)

Continued ▶

Leptospirosis Management

Once leptospirosis diagnosis is confirmed, patients should be treated with antimicrobials and supportive care as needed.

Antimicrobials

- If the patient can tolerate oral medication: Doxycycline (5 mg/kg PO every 12 hours) for 14 days[1])
- If the patient cannot tolerate oral medication: Ampicillin (20 mg/kg IV every 6 hours), then, if possible, de-escalated to oral doxycycline (5 mg/kg PO every 12 hours) for an additional 14 days[1]

Supportive Care

- IV fluids for replacement, diuresis, acid-base balance, and electrolyte maintenance
- Antiemetics
- Nutritional support for renal or hepatic injury
- Renal replacement therapy can be considered in oliguric dogs developing volume overload, severe hyperkalemia, or severe azotemia nonresponsive to medical management.[1]
- Other care as needed based on clinical syndrome and patient response to treatment

During hospitalization, hydration status should be carefully monitored (ie, measure "ins and outs," thoracic auscultation, blood pressure), as should BUN/creatinine, acid-base/electrolytes, ± hepatic enzymes (as often as every 24 hours initially). PCV should be rechecked as often as every 24 hours initially, and CBC should be repeated as often as every 48 hours if thrombocytopenia is present and/or in severe cases. Urine specific gravity should also be rechecked every few days once fluid therapy has been discontinued, and clotting factors should be rechecked if abnormal.

Approximately 1 week after the patient is discharged, serum chemistry profile should be repeated, as should CBC if abnormalities were present at the time of discharge. Serum chemistry profile should be rechecked again in 3 to 7 days if results are still abnormal. Urine specific gravity should be monitored regularly if abnormal.

TABLE

LEPTOSPIROSIS TESTS & CONSIDERATIONS

Test	Target	Sample type	Patient-side?	Impacted by vaccination?	Impacted by antimicrobial treatment?
MAT	Antibody (IgM and IgG)	Serum	No	Yes	No
Lepto rapid test	Antibody (IgM)	Serum	Yes	Yes	No
LipL-32 Leptospira	Antibody (IgG>IgM)	Serum	Yes	Yes	No
PCR	Antigen	Urine, whole blood	No	No	Potentially

Reference

1. Sykes JE, Hartmann K, Lunn KF, Moore GE, Stoddard RA, Goldstein RE. 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2011;25(1):1-13.

Suggested Reading

Barr SC, McDonough PL, Scipioni-Ball RL, Starr JK. Serologic responses of dogs given a commercial vaccine against *Leptospira interrogans* serovar pomona and *Leptospira kirschneri* serovar grippotyphosa. *Am J Vet Res*. 2005;66(10):1780-1784.

Curtis KM, Foster PC, Smith PS, et al. Performance of a recombinant LipL32 based rapid in-clinic ELISA (SNAP Lepto) for the detection of antibodies against Leptospira in dogs. *Intern J Appl Res Vet Med*. 2015;13(3):182-189.

Lizer J, Grahlmann M, Hapke H, Velineni S, Lin D, Kohn B. Evaluation of a rapid IgM detection test for diagnosis of acute leptospirosis in dogs. *Vet Rec*. 2017;180(21):517.

Lizer J, Velineni S, Weber A, Krecic M, Meeus P. Evaluation of 3 serological tests for early detection of Leptospira-specific antibodies in experimentally infected dogs. *J Vet Intern Med*. 2018;32(1):201-207.

Midence JN, Leutenegger CM, Chandler AM, Goldstein RE. Effects of recent Leptospira vaccination on whole blood real-time PCR testing in healthy client-owned dogs. *J Vet Intern Med*. 2012;26(1):149-152.

Schuller S, Francey T, Hartmann K, et al. European consensus statement on leptospirosis in dogs and cats. *J Small Anim Pract*. 2015;56(3):159-179.

IgG = immunoglobulin G

IgM = immunoglobulin M

MAT = microscopic agglutination test

Elura™

(capromorelin oral solution)

20 mg/mL
For oral use in cats only

CAUTION:
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Before using Elura, please consult the product insert, a summary of which follows:

INDICATION:
For management of weight loss in cats with chronic kidney disease.

DOSAGE AND ADMINISTRATION:
Administer ELURA orally at a dose of 2 mg/kg (0.9 mg/lb) or 0.1 mL/kg (0.045 mL/lb) body weight once daily.

CONTRAINDICATIONS:
ELURA should not be used in cats that have a hypersensitivity to capromorelin.

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 oral use in cats only.
Do not use in cats with hypersomatotropism (acromegaly). ELURA may increase serum glucose for several hours after dosing. Use in cats with current or historical diabetes mellitus has not been evaluated and use may not be appropriate.

PRECAUTIONS:
Use with caution in cats that may have cardiac disease or severe dehydration. ELURA causes transient decreases in heart rate and blood pressure up to 4 hours following dose administration. Some cats may exhibit clinical signs of bradycardia or hypotension following administration of ELURA. Use with caution in cats with hepatic dysfunction. Capromorelin is metabolized in the liver in humans and dogs and similar metabolism is expected in the cat.
The safe use of ELURA has not been evaluated in cats younger than 5 months old. The safe use of ELURA has not been evaluated in cats that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS:
Safety was evaluated in a 56-day field effectiveness study in 176 client-owned cats (118 administered ELURA, 58 administered vehicle control) that received at least one dose. Cats enrolled had ≥5% unintended weight loss and a history of chronic kidney disease (CKD). Cats had a mean age of 15 years and at enrollment 11.4% of the cats were in Stage 1 CKD, 66.5% were in Stage 2, 21.0% were in Stage 3, and 1.1% were in Stage 4. Cats enrolled in the study had a variety of comorbid conditions: dental disease (88.1%), moderate or severe muscle loss (43.2%), heart murmur (28.4%), history of vomiting or underlying gastrointestinal disease (28.4%), hyperthyroidism (13.6%) and hypertension (9.7%).

Table 1: Adverse Reactions in the Field Effectiveness Study

Adverse Reaction	ELURA (n=118)	Vehicle Control (n=58)
Vomiting	35 (29.6%)	13 (22.4%)
Hypersalivation	25 (21.2%)	0 (0.0%)
Inappetence	22 (18.6%)	7 (12.0%)
Behavior Change [a]	17 (14.4%)	3 (5.2%)
Lethargy	16 (13.6%)	6 (10.3%)
Anemia	11 (9.3%)	1 (1.7%)
Dehydration	11 (9.3%)	2 (3.4%)
Stage of CKD Increased [b]	10 (8.5%)	3 (5.2%)
Diarrhea	9 (7.6%)	2 (3.4%)
Urinary Tract Infection	8 (6.8%)	2 (3.4%)
Hyperglycemia	8 (6.8%)	2 (3.4%)
Upper Respiratory Infection	7 (5.9%)	1 (1.7%)
Hypercalcemia	7 (5.9%)	0 (0.0%)

Adverse Reaction	ELURA (n=118)	Vehicle Control (n=58)
Facial Skin Lesion	6 (5.1%	3 (5.2%)
Hyperkalemia	5 (4.2%)	0 (0.0%)
Ataxia	4 (3.4%)	0 (0.0%)
Diabetes Mellitus	1 (0.8%)	0 (0.0%)
Congestive Heart Failure	1 (0.8%)	0 (0.0%)

Note: If an animal experienced the same event more than once, only the first occurrence was tabulated.
[a] Behavior change included hiding from the owner (8 ELURA, 1 vehicle control); owner reported difficulty administering medication (7 ELURA, 1 vehicle control); and redirected aggression to another household cat (2 ELURA, 1 vehicle control).
[b] Two ELURA and 1 vehicle control cat increased by two CKD stages; 8 ELURA and 2 vehicle control cats increased one CKD stage. It could not be determined if the progressive renal disease was the natural course of the pre-existing disease or treatment related.
Hypersalivation was generally associated with dosing and resolved within a few minutes.
Nine cats (8 ELURA and 1 vehicle control) either died or were euthanized during or shortly after the study. Six ELURA cats were euthanized or died from decompensated CKD. One ELURA cat was euthanized after study withdrawal on Day 33 for declining quality of life and recent identification of a new mass. One ELURA cat acutely declined and was euthanized for findings of nodules in both kidneys and diagnosis of sarcoma. The vehicle control cat was euthanized for acute onset of right hindlimb paresis and suspected embolic event. Two additional cats were diagnosed with neoplasia during the study (one ELURA cat with unspecified soft tissue sarcoma and one control cat with mammary adenocarcinoma) but completed the study. In voluntary post-approval reporting for extra-label use of a capromorelin product for dogs, the following adverse events have been reported in cats (listed in decreasing order of reporting frequency): bradycardia, lethargy, hypersalivation, hypotension, behavior change, and vomiting.
To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US, Inc. at 1-888-545-5973.
For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

EFFECTIVENESS:
Effectiveness was demonstrated in a multicenter, prospective, masked, randomized, vehicle-controlled field study. The study enrolled 176 client-owned cats with ≥5% unintended weight loss and a history of chronic kidney disease. The cats enrolled included 96 females and 80 males of various breeds, 4.4 - 22.1 years old with a mean age of 15 years and weighing 1.81 - 6.76 kg. CKD stage was determined based on creatinine at screening according to the International Renal Interest Society (IRIS) 2015 guidelines. All stages were enrolled. Cats were administered ELURA at 2 mg/kg or a matched volume of control once daily by mouth for 56 days. The control was the solution without capromorelin (vehicle control). The primary effectiveness variable was the percent change in body weight from Day 0 to Day 55. Effectiveness was evaluated in 112 cats: 71 cats administered ELURA and 41 cats administered vehicle control. There was a statistically significant difference between the percent change in weight for the ELURA group (+5.2%) compared to the vehicle control group (-1.6%) at Day 55 ($p<0.0001$). Secondary analysis for percent change in weight at Day 15 and Day 27 demonstrated cats in the ELURA group gained weight throughout the study.

STORAGE CONDITIONS:
Store at or below 86°F (30°C)

HOW SUPPLIED:
20 mg/mL flavored oral solution in a 15 mL bottle with an oral dosing syringe.
Approved by FDA under NADA # 141-536.
Manufactured for: Elanco US Inc, Greenfield, IN 46140 USA
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Elura™
(capromorelin oral solution)

Elura helps cats with CKD maintain or gain weight to keep them

feline fabulous

It can be hard to watch cats with chronic kidney disease (CKD) waste away. Prescribe Elura at the first sign of weight loss in your feline CKD patients.

- MORE THAN 8/10 CATS GAINED WEIGHT*[1]
- UNIQUE MOA MIMICS THE NATURALLY OCCURRING HORMONE GHRELIN
- SAFE TO USE DAILY AND APPROVED FOR LONG-TERM USE
- ORAL SOLUTION WITH LOW DOSING VOLUME

INDICATION

For the management of weight loss in cats with chronic kidney disease.

IMPORTANT SAFETY INFORMATION

For oral use in cats only. Do not use in cats that have a hypersensitivity to capromorelin, or in cats with hypersomatotropism (acromegaly). Elura may increase serum glucose for several hours after dosing; use in cats with current or historical diabetes mellitus has not been evaluated and may not be appropriate. Use with caution in cats that may have cardiac disease, severe dehydration, or hepatic dysfunction. Elura has not been evaluated in cats younger than 5 months of age, or in breeding, pregnant or lactating cats. The most common adverse reactions included vomiting, hypersalivation, inappetence, behavior change and lethargy. Please see accompanying brief summary for product safety information.

***Compared to 4/10 control cats. A multi-center, placebo-controlled, randomized and masked field study including 176 cats with CKD and at least 5% unintended loss of body weight (as compared to the highest weight in the medical records for the 3 years preceding enrollment). Study period was 56 days (Day 0 – Day 55). Primary endpoint was percent change in weight from Day 0 to Day 55.**
CKD, chronic kidney disease.

1. Elura Freedom of Information Summary. NADA 141-536. 2020.
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PM-US-20-2838

See page 29 for product information summary.

Elanco™

Proteinuria in Dogs

Barry Hedgespeth, BVSc
Karyn Harrell, DVM, DACVIM
North Carolina State University

Following are differential diagnoses for dogs presented with proteinuria.

Prerenal

- Hemoglobinuria
- Myoglobinuria
- Light chain immunoglobulins (multiple myeloma, lymphoma)

Renal

- Functional or physiologic
  - Congestive heart failure
  - Strenuous exercise
  - Fever
  - Seizure
  - Exposure to extreme temperatures
- Glomerular
  - Infection
    - –Bacterial (eg, anaplasmosis, borreliosis, bartonellosis, brucellosis, endocarditis, pyelonephritis, pyometra, pyoderma, Rocky Mountain spotted fever, other chronic infections)
    - –Protozoal (eg, babesiosis, hepatozoonosis, leishmaniasis, trypanosomiasis)
    - –Viral (eg, canine adenovirus type 1)
    - –Parasitic (eg, dirofilariasis, schistosomiasis)
    - –Fungal (eg, blastomycosis, coccidioidomycosis, histoplasmosis, phaeohyphomycosis)
  - Inflammatory
    - –Chronic dermatitis
    - –Inflammatory bowel disease
    - –Acute pancreatitis
    - –Periodontal disease
    - –Polyarthritis
    - –Systemic lupus erythematosus
    - –Other immune-mediated disease
  - Neoplastic
    - –Leukemia
    - –Lymphoma
    - –Mastocytosis
    - –Primary erythrocytosis/polycythemia vera
    - –Systemic histiocytosis
  - Congenital or familial
    - –Amyloidosis (eg, beagle, English foxhound, shar-pei)
    - –Hereditary nephritis (eg, bull terrier, cocker spaniel, Dalmatian, Samoyed)
    - –Podocytopathy (soft-coated wheaten terrier)
    - –Membranoproliferative glomerulonephritis (Bernese mountain dog)
    - –Atrophic glomerulopathy (rottweiler)
  - Miscellaneous
    - –Corticosteroids (endogenous/spontaneous hyperadrenocorticism or exogenous)
    - –Diabetes mellitus
    - –Systemic hypertension
    - –Hyperlipidemia
    - –Drug reactions (eg, sulfonamide [eg, sulfa-/trimethoprim] therapy, masitinib)
    - –Chronic insulin infusion
    - –Congenital C3 deficiency
    - –Cyclic hematopoiesis (ie, gray collie syndrome)
- Tubulointerstitial
  - Chronic kidney disease (including congenital/familial conditions such as renal dysplasia and polycystic kidney disease)
  - Acute kidney injury
    - –Leptospirosis
    - –Toxins (eg, NSAIDs, grapes, raisins, currants, ethylene glycol, vitamin D3, aminoglycosides, amphotericin B, sulfonamide [eg, sulfa-/trimethoprim] therapy, tyrosine kinase inhibitors [toceranib phosphate, masitinib mesylate] heavy metal ingestion [eg, lead, mercury, arsenic, thallium], insect or snake bite)
  - Fanconi syndrome
  - Interstitial nephritis

Postrenal

- Urinary
  - Bacterial cystitis
  - Urolithiasis
  - Neoplasia (eg, urothelial carcinoma)
- Extra-urinary
  - Prostatitis
  - Vaginitis
  - Pyometra

See page 73 for references.

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FROM PAGE TO PATIENT

Designed to bridge the gap between research pages and daily practice protocol, the following pearls offer tips and techniques to grow the general practitioner's clinical excellence.

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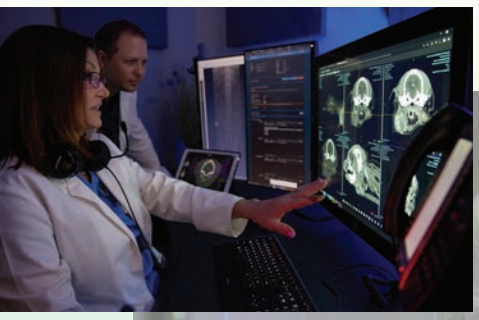

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Comparing Bacterial Communities on Skin of Healthy & Allergic Cats

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Monona, Wisconsin

In the literature

Older CE, Diesel AB, Starks JM, Lawhon SD, Hoffmann AR. Characterization of staphylococcal communities on healthy and allergic feline skin. *Vet Dermatol*. 2021;32(1):61-e10.

FROM THE PAGE ...

Relatively little is known about the normal microbial populations on the skin of cats as compared with that of humans and dogs. In this study, researchers investigated the staphylococcal communities on the skin of healthy and allergic cats. Skin swabs were obtained from the ear canal and groin of 11 healthy cats and 10 allergic cats. Skin samples from allergic cats were free of skin lesions. DNA was extracted from the samples and sequenced using a region of the 16S rRNA gene. Predominant phyla found included Proteobacteria (average relative abundance 52.29%), Firmicutes (17.94%), Actinobacteria (13.99%), and Bacteroidetes (11.87%). Overall abundance of *Staphylococcus* spp was fairly low, with an average abundance of 4.34% in healthy cats and 3.61% in allergic cats. Samples with staphylococcal sequences often had multiple different species, with an average of 2 species per sample. *S epidermidis* and *S pseudintermedius* were most common in samples from healthy cats, and *S capitis* and *S felis* were most common in samples from allergic cats. *S pseudintermedius* was only identified in 4 sequences from allergic cats. No significant difference in microbial diversity was found between healthy and allergic cats.

... TO YOUR PATIENTS

Key pearls to put into practice:

1. Diverse populations of *Staphylococcus* spp exist in cats. This differs from dogs, in which *S pseudintermedius* is the predominant species found in both healthy and allergic patients. This finding provides evidence for different clinical considerations in management of dogs and cats.

2. Differences in flora detected between healthy and allergic patients may represent targets for therapeutic intervention. In this study, significant differences were not found in the cutaneous microbiota of healthy and allergic cats; however, because the study sampled nonlesional skin of allergic cats, it is possible that lesional skin of allergic cats may have different microbiota.

3. Although statistical significance was not achieved, some differences were observed between healthy and allergic feline skin. *S epidermidis* was more common on the skin of healthy cats as compared with allergic cats. This is also found in humans, in which *S epidermidis* is more common on healthy human skin and can have a protective role in skin health.[1] Further research is needed to determine if a similar protective role can be documented in cats.

Reference

1. Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. *J Invest Dermatol*. 2011;131(10):1974-1980.

MERCK
Animal Health

sentinel® spectrum® chews

(milbemycin oxime·lufenuron·praziquantel)

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: SENTINEL® SPECTRUM® Chews are available in four strengths in color-coded packages for oral administration to dogs and puppies according to their weight. Each chewable flavored tablet is formulated to provide a minimum of 0.23 mg/pound (0.5mg/kg) of milbemycin oxime, 4.55 mg/pound (10mg/kg) of lufenuron, and 2.28 mg/pound (5mg/kg) of praziquantel.

Milbemycin oxime consists of the oxime derivatives of 5-didehydromilbemycins in the ratio of approximately 80% A_4 ($C_{32}H_{45}NO_7$, MW 555.71) and 20% A_3 ($C_{31}H_{43}NO_7$, MW 541.68). Milbemycin oxime is classified as a macrocyclic anthelmintic.

Lufenuron is a benzoylphenylurea derivative with the following chemical composition: N-[2,5-dichloro-4-(1,1,2,3,3,3,-hexafluoropropoxy)-phenyl-aminocarbonyl]-2,6-difluorobenzamide ($C_{17}H_8Cl_2F_8N_2O_3$, MW 511.15). Benzoylphenylurea compounds, including lufenuron, are classified as insect development inhibitors (IDIs).

Praziquantel is an isoquinolone anthelmintic with the chemical name 2-(Cyclohexylcarbonyl)-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one.

Indications: SENTINEL SPECTRUM Chews are indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*; for the prevention and control of flea populations (*Ctenocephalides felis*); and for the treatment and control of adult roundworm (*Toxocara canis, Toxascaris leonina*), adult hookworm (*Ancylostoma caninum*), adult whipworm (*Trichuris vulpis*), and adult tapeworm (*Dipylidium caninum, Taenia pisiformis, Echinococcus multilocularis* and *Echinococcus granulosus*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

Dosage and Administration: SENTINEL SPECTRUM Chews should be administerd orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, 4.55 mg/lb (10 mg/kg) lufenuron, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes (see **EFFECTIVENESS**).

Dosage Schedule

Body Weight	Milbemycin Oxime per chewable	Lufenuron per chewable	Praziquantel per chewable	Number of chewables
2 to 8 lbs.	2.3 mg	46 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	115 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	230 mg	114 mg	One
50.1 to 100 lbs.	23.0 mg	460 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables			

To ensure adequate absorption, always administer SENTINEL SPECTRUM Chews to dogs immediately after or in conjunction with a normal meal.

SENTINEL SPECTRUM Chews may be offered to the dog by hand or added to a small amount of dog food. The chewables should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole. Care should be taken that the dog consumes the complete dose, and treated animals should be observed a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

Heartworm Prevention: SENTINEL SPECTRUM Chews should be administered at monthly intervals beginning within one month of the dog's first seasonal exposure to mosquitoes and continuing until at least 6 months after the dog's last seasonal exposure (see **EFFECTIVENESS**). SENTINEL SPECTRUM Chews may be administered year-round without interruption. When switching from another heartworm preventative product to SENTINEL SPECTRUM Chews, the first dose of SENTINEL SPECTRUM Chews should be given within a month of the last dose of the former product.

Flea Treatment and Prevention: Treatment with SENTINEL SPECTRUM Chews may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of flea season. In areas where fleas are common year-round, monthly treatment with SENTINEL SPECTRUM Chews should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea protection product, as necessary.

Intestinal Nematode and Cestode Treatment and Control: Dogs may be exposed to and can become infected with roundworms, whipworms, hookworms, and tapeworms throughout the year, regardless of season or climate. Clients should be advised of appropriate measures to prevent reinfection of their dog with intestinal parasites. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Contraindications: There are no known contraindications to the use of SENTINEL SPECTRUM Chews.

Warnings: Not for use in humans. Keep this and all drugs out of the reach of children.

Precautions: Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see **EFFECTIVENESS**).

Prior to administration of SENTINEL SPECTRUM Chews, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. SENTINEL SPECTRUM Chews are not effective against adult *D. immitis*.

Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Do not use in puppies less than six weeks of age.

Do not use in dogs or puppies less than two pounds of body weight.

The safety of SENTINEL® SPECTRUM® Chews has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime and lufenuron alone (see **ANIMAL SAFETY**).

Adverse Reactions: The following adverse reactions have been reported in dogs after administration of milbemycin oxime, lufenuron, or praziquantel: vomiting, depression/lethargy, pruritus, urticaria, diarrhea, anorexia, skin congestion, ataxia, convulsions, salivation, and weakness.

To report suspected adverse drug events, contact Merck Animal Health at 1-800-224-5381. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

For technical assistance, call Merck Animal Health at 1-800-224-5318.

Information for Owner or Person Treating Animal: *Echinococcus multilocularis* and *Echinococcus granulosus* are tapeworms found in wild canids and domestic dogs. *E. multilocularis* and *E. granulosus* can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where *E. multilocularis* or *E. granulosus* are endemic should be instructed on how to minimize their risk of exposure to these parasites, as well as their dog's risk of exposure. Although SENTINEL SPECTRUM Chews were 100% effective in laboratory studies in dogs against *E. multilocularis* and *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Effectiveness

Heartworm Prevention: In a well-controlled laboratory study, SENTINEL SPECTRUM Chews (*milbemycin oxime, lufenuron, praziquantel*) were 100% effective against induced heartworm infections when administered once monthly for 6 consecutive months. In well-controlled laboratory studies, neither one dose nor two consecutive doses of SENTINEL SPECTRUM Chews provided 100% effectiveness against induced heartworm infections.

Intestinal Nematodes and Cestodes Treatment and Control: Elimination of the adult stage of hookworm (*Ancylostoma caninum*), roundworm (*Toxacara canis, Toxascaris leonina*), whipworm (*Trichuris vulpis*) and tapeworm (*Dipylidium caninum, Echinococcus multilocularis, Echinococcus granulosus, Taenia pisiformis*) infections in dogs was demonstrated in well-controlled laboratory studies.

Flea Prevention and Control: In well-controlled studies, SENTINEL SPECTRUM Chews were effective in preventing flea eggs from hatching, thus providing control of the development of flea populations (*Ctenocephalides felis*).

Palatability: In a field study of 117 dogs offered SENTINEL SPECTRUM Chews, 113 dogs (96.6%) accepted the product when offered from the hand as if a treat, 2 dogs (1.7%) accepted it from the bowl with food, 1 dog (0.9%) accepted it when it was placed in the dog's mouth, and 1 dog (0.9%) refused it.

Animal Safety: In a margin of safety study, 40 ten-week-old puppies (10 per group) were administered either a sham dose (0X) or doses of 1, 3, or 5X the maximum exposure dose of SENTINEL SPECTRUM Chews once every two weeks for a total of seven treatments. Transient ataxia, lethargy, tremors, and salivation were seen in the 3X and 5X groups following each of the seven doses. Lethargy and ataxia were occasionally reported in sham-dosed (0X) and 1X dogs. Tremors were observed twice post-treatment in the 1X treatment group. Vomiting was seen in all treatment groups but at a higher incidence in the 3X and 5X groups. At the 5X dose, shallow breathing was noted in two dogs and one dog was unable to stand following two different doses. All clinical signs resolved within 24 hours.

In a second margin of safety study, 64 six-week-old puppies (16 per group) were dosed with either a sham (0X) or 1, 3, or 5X the maximum exposure dose of SENTINEL SPECTRUM Chews on days 1, 15, 29, and 43. A dose dependent increase in ataxia, decreased activity, tremors, and salivation was seen within 24 hours of treatment. Splayed hind limbs were observed once in one dog in the 5X treatment group. Vomiting was observed in the 5X treatment group.

For SENTINEL SPECTRUM Chews, the maximum exposure based on product dosing is 2.5 mg/kg for milbemycin oxime, 50.7 mg/kg for lufenuron and 25.1 mg/kg for praziquantel, which is higher than the minimum effective dose used in the safety studies for milbemycin oxime and lufenuron (see below).

Milbemycin Oxime: Two studies were conducted in heartworm-infected dogs treated with milbemycin oxime. Mild, transient hypersensitivity reactions were observed in dogs with high microfilariae counts (see **PRECAUTIONS**).

Safety studies in pregnant dogs demonstrated that doses of 0.6X the maximum exposure dose of SENTINEL SPECTRUM Chews, (1.5 mg/kg of milbemycin oxime), administered daily from mating through weaning, resulted in measurable concentrations of milbemycin oxime in milk. Puppies nursing these females demonstrated milbemycin oxime-related effects (depression, decreased activity, diarrhea, dehydration, nasal discharge). A subsequent study, which evaluated the daily administration of 0.6X the maximum exposure dose of SENTINEL SPECTRUM Chews, from mating until one week before weaning, demonstrated no effects on the pregnant females or their litters. A study, in which pregnant females were dosed once, at 0.6X maximum exposure dose of SENTINEL SPECTRUM Chews before, on the day of, or shortly after whelping, resulted in no effects on the puppies.

Some nursing puppies, at 2, 4, and 6 weeks of age, administered oral doses of 9.6 mg/kg milbemycin oxime (3.8X the maximum exposure dose of SENTINEL SPECTRUM Chews) exhibited tremors, vocalization, and ataxia. These effects were all transient and puppies returned to normal within 24 to 48 hours. No effects were observed in puppies administered 0.5 mg/kg milbemycin oxime (minimum label dose).

A rising-dose safety study conducted in rough-coated Collies resulted in ataxia, pyrexia, and periodic recumbency in one of fourteen dogs administered milbemycin oxime at 12.5 mg/kg (5X the maximum exposure dose of SENTINEL SPECTRUM Chews). Prior to receiving the 12.5 mg/kg dose on day 56 of the study, all animals had undergone a dosing regimen consisting of 2.5 mg/kg milbemycin oxime on day 0, followed by 5.0 mg/kg on day 14, and 10.0 mg/kg on day 32. No adverse reactions were observed in any of the Collies treated with doses less than 12.5 mg/kg.

Lufenuron: In a ten-month study, doses of lufenuron up to 2X the maximum exposure dose of SENTINEL SPECTRUM Chews (10 mg/kg) caused no overt toxicity. A single dose of 200 mg/kg had no marked effect on adult dogs, but caused decreased activity and reduced appetite in eight-week-old puppies. Lufenuron tablets were evaluated with concurrent administration of flea adulticides containing carbaryl, permethrin, chlorpyriphos, and cythioate. No toxicty resulted from these combinations. Lufenuron tablets did not cause cholinesterase inhibition nor did they enhance cholinesterase inhibition caused by exposure to organophoshphates.

Two laboratory and two well-controlled field studies were conducted to evaluate reproductive safety of lufenuron tablets in breeding dogs. In one of the laboratory studies, in which lufenuron was administered to Beagle dogs as three divided doses, equivalent to 17.8X the maximum exposure dose of SENTINEL SPECTRUM Chews (10 mg/kg), the ratio of gravid females to females mated was 8/8 or 100% in the control group and 6/9 or 67% in the lufenuron-treated group. The mean number of pups per litter was two animals higher in the lufenuron versus control groups and mean birth weights of pups from treated females in this study was lower than control groups. These pups grew at a similar rate to the control pups. The incidence of nasal discharge, pulmonary congestion, diarrhea/dehydration, and sluggishness was higher in the lufenuron-treated pup group than in the control pup group. The incidence of these signs was transient and decreasing by the end of lactation.

Results from three additional reproductive safety studies, one laboratory and two field studies, evaluating eleven breeds of dogs, did not demonstrate any adverse findings for the reproductive parameters measured, including fertility, pup birth weights, and pup clinical signs, after administration of lufenuron up to 1X the maximum exposure dose of SENTINEL SPECTRUM Chews. The average milk: blood concentration ratio was approximately 60 (i.e. 60X higher drug concentrations in the milk compared to drug levels in the blood of treated females). Nursing puppies averaged 8-9 times higher blood concentrations of lufenuron compared to their dams.

Storage Information: Store in a dry place at controlled room temperature, between 59° and 77°F (15-25°C).

How Supplied: SENTINEL SPECTRUM Chews are available in four strengths, formulated according to the weight of the dog. Each strength is available in color-coded packages of six chewable tablets each.

Manufactured for: Intervet Inc (d/b/a Merck Animal Health)
2 Giralda Farms
Madison, NJ 07940

Approved by FDA under NADA # 141-333

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IMPORTANT SAFETY INFORMATION:

SENTINEL® SPECTRUM® Chews (milbemycin oxime/lufenuron/praziquantel). Dogs should be tested for heartworm prior to use. Mild hypersensitivity reactions have been noted in some dogs carrying a high number of circulating microfilariae. Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention. For complete product information refer to the product insert on page 36.

*SENTINEL SPECTRUM Chews protects against heartworm disease, 4 intestinal parasites, and prevents flea eggs from hatching.
†*A. caninum.*
‡Prevents flea eggs and maggot-like larvae from developing.

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MERCK Animal Health

Sedation in African Pygmy Hedgehogs

Angela M. Lennox, DVM, DABVP (Avian, Exotic Companion Mammal), DECZM (Small Mammal)
Avian & Exotic Animal Clinic
Indianapolis, Indiana

In the literature

Hawkins SJ, Doss GA, Mans C. Evaluation of subcutaneous administration of alfaxalone-midazolam and ketamine-midazolam as sedation protocols in African pygmy hedgehogs (*Atelerix albiventris*). *J Am Vet Med Assoc*. 2020;257(8):820-825.

FROM THE PAGE ...

African pygmy hedgehogs almost always require immobilization to undergo complete physical examination. This species is prone to neoplasia[1,2]; thus, examination should be thorough and include careful inspection of the oral cavity, as well as abdominal palpation.

Anecdotally, immobilization is often accomplished via chamber induction with inhalation agents. Although chamber induction may seem safe, it can be stressful in many species (including rodents and rabbits) and can increase staff exposure to anesthetic waste gas.[3] Clinician resistance to injectable sedative agents may be due to perceived difficulties in injecting conscious hedgehogs or the desire to limit time between presentation and discharge.

This blinded crossover study compared 2 SC sedation protocols in hedgehogs: ketamine (30 mg/kg) in conjunction with midazolam (1 mg/kg) and alfaxalone (3 mg/kg) in conjunction with midazolam (1 mg/kg). Various physiological parameters were measured. Flumazenil (0.05 mg/kg SC) was administered 45 minutes after sedation for midazolam reversal. Although SC administration was not discussed, SC and intramantle injection are typically easy to accomplish (***Figure***).

Both protocols resulted in sedation levels that would likely allow for thorough physical examination and optimal positioning for diagnostic imaging. Time to loss of righting response, duration of effects, and recovery time after flumazenil administration did not differ significantly.

Sedation with ketamine and midazolam was less consistent than with alfaxalone and midazolam, as not every patient completely lost the righting response, and there were more pronounced effects on body weight and food intake in the 6 days after sedation. Further, because of ketamine's acidic pH, this drug can cause more pain on injection as compared with alfaxalone.

▲ **FIGURE** Intramantle injection of a combination of drugs used for sedation in an African pygmy hedgehog

… TO YOUR PATIENTS

Key pearls to put into practice:

1. A complete physical examination in African pygmy hedgehogs almost always requires immobilization. Thorough examination is essential because of the species' high incidence of neoplasia.
2. Although inhalation agents via chamber induction are commonly used for sedation, injectable agents are a viable option that likely reduce stress and decrease staff exposure to anesthetic waste gas.
3. Both protocols discussed in this study provided adequate sedation for thorough physical examination and, likely, optimal positioning for diagnostic imaging and were apparently safe.
4. The author uses alfaxalone (1-3 mg/kg), midazolam (0.5-1 mg/kg), and butorphanol (0.2 mg/kg) for sedation, with additional 1 mg/kg alfaxalone boluses as indicated. Although recovery is not as rapid as with inhalation chamber induction, most patients are ready for discharge within 30 to 45 minutes after reversal with flumazenil.

References

1. Okada K, Kondo H, Sumi A, Kagawa Y. A retrospective study of disease incidence in African pygmy hedgehogs (*Atelerix albiventris*). *J Vet Med Sci.* 2018;80(10):1504-1510.
2. Del Aguila G, Torres CG, Carvallo FR, Gonzalez CM, Cifuentes FF. Oral masses in African pygmy hedgehogs. *J Vet Diagn Invest*. 2019;31(6):864-867.
3. Hohlbaum K, Bert B, Dietze S, Palme R, Funk H, Thöne-Reineke C. Severity classification of repeated isoflurane anesthesia in C57BL/6JRj mice–assessing the degree of distress. *PLoS ONE*. 2017;12(6):e0179588.

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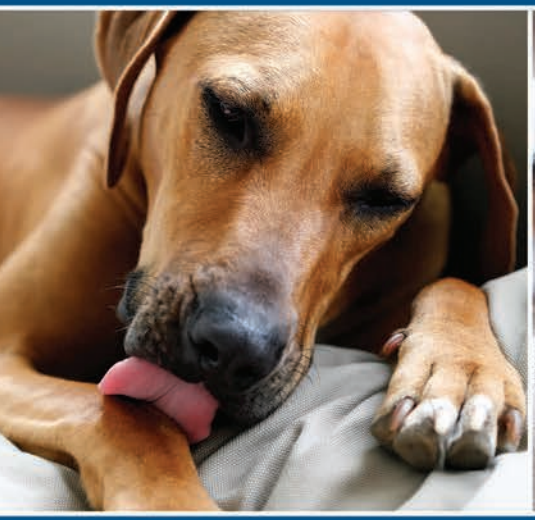

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[1] Mesman, Mollie, et al. Residual antibacterial activity of canine hair treated with topical antimicrobial sprays against *Staphylococcus pseudintermedius* in vitro. Vet Dermatol 2016, 27, 261-e61.

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Potential Novel Treatment for Canine Pemphigus Foliaceus

William Oldenhoff, DVM, DACVD
Madison Veterinary Specialists
Monona, Wisconsin

In the literature

Goodale EC, White SD, Bizikova P, et al. Open trial of Bruton's tyrosine kinase inhibitor (PRN1008) in the treatment of canine pemphigus foliaceus. *Vet Dermatol.* 2020;31(5):410-e110.

FROM THE PAGE …

This study* evaluated the efficacy of a Bruton's tyrosine kinase (BTK) inhibitor in the treatment of canine pemphigus foliaceus. BTK is necessary for B-cell development, and autoreactive B cells are particularly dependent on BTK for survival as compared with normal B cells.[1] Autoreactive B cells produce autoantibodies, which contribute to various autoimmune diseases. Canine pemphigus foliaceus is characterized by production of antibodies directed primarily against desmocollin-1, a component of desmosomes. When BTK is absent, autoantibodies are lost and total antibody levels are unchanged. Because of this targeted effect, BTK inhibition is an appealing candidate in the treatment of humorally mediated autoimmune diseases (eg, pemphigus foliaceus).

The BTK inhibitor, BTKi PRN1008 (also called rilzabrutinib), was evaluated in the treatment of 4 dogs with pemphigus foliaceus. Initial doses of 15 mg/kg PO once daily were used, with administration increased to twice daily if inadequate response was noted. Final daily doses were in the range between 17 mg/kg and 33 mg/kg. All dogs showed improvement within the first 2 weeks of treatment, and 3 dogs were near remission by 20 weeks. The remaining dog achieved a fair response. After treatment, anti-desmocollin-1 immunoglobulin G was measured and determined to be absent in 2 dogs, reduced in 1 dog, and uninterpretable in 1 dog. An 8-year-old intact female developed pyometra during the study, but it is not clear whether this was related to rilzabrutinib. The same dog had elevated ALT and AST, both of which returned to normal when the dose was decreased.

*This study was funded by Principia Biopharma.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Pemphigus foliaceus is a challenging disease to treat. In most cases, high doses of systemic steroids are needed to induce remission. This is typically followed by a gradual dose reduction to the lowest steroid dose that maintains remission of disease. Frequently, nonsteroidal immunosuppressive drugs are also used to allow further reduction of the steroid dose.
2. Steroids have a variety of common adverse effects, which can be challenging to manage, especially in patients that require ongoing immunosuppression, as is the case in most dogs with pemphigus foliaceus. Nonsteroidal immunosuppressive drugs also have the potential for serious adverse effects. Thus, there is a need for novel targeted therapies in dogs with pemphigus foliaceus.
3. Rilzabrutinib is promising, as it was able to induce remission in 3 of the 4 study dogs. There were few adverse effects, but the study was limited by the small number of dogs enrolled. In addition, the study took place over 20 weeks, but most dogs with pemphigus foliaceus require ongoing, lifelong therapy. It is not known whether longer courses of rilzabrutinib may be associated with more adverse effects. Further study will be needed to determine if rilzabrutinib is a good long-term alternative to steroids in the treatment of pemphigus foliaceus.

Reference

1. Crofford LJ, Nyhoff LE, Sheehan JH, Kendall PL. The role of Bruton's tyrosine kinase in autoimmunity and implications for therapy. *Expert Rev Clin Immunol*. 2016; 12(7):763-773.

GALLIPRANT® (grapiprant tablets)

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Caution:
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Before using Galliprant, 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.

Only the 20 mg and 60 mg tablets of GALLIPRANT are scored. The dosage should be calculated in half tablet increments. Dogs less than 8 lbs. (3.6 kgs) cannot be accurately dosed.

The 100 mg tablet is not scored and should not be broken in half.

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:

Table 1. Adverse reactions reported in the field study.

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 to 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.[7] 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 and 100 mg flavored tablets in 7, 30 and 90 count bottles

NADA 141-455, Approved by FDA

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140

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November 2018

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- **MODE OF ACTION TARGETS** canine OA pain and inflammation while reducing the impact on GI, kidney, and liver homeostasis[1,2‡]
- **FOR ALL STAGES** of OA from the earliest clinical signs*

*Approved for use in dogs older than 9 months of age and greater than 8 pounds.
‡Monitoring is recommended if used long-term.

Simple, once-daily chewable tablet

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INDICATION
Galliprant is an NSAID that controls pain and inflammation associated with osteoarthritis in dogs.

IMPORTANT SAFETY INFORMATION
Not for use in humans. For use in dogs only. Keep this and all medications out of reach of children and pets. Store out of reach of dogs and other pets in a secured location in order to prevent accidental ingestion or overdose. Do not use in dogs that have a hypersensitivity to grapiprant. If Galliprant is used long term, appropriate monitoring is recommended. Concomitant use of Galliprant with other anti-inflammatory drugs, such as COX-inhibiting NSAIDs or corticosteroids, should be avoided. Concurrent use with other anti-inflammatory drugs or protein-bound drugs has not been studied. 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, pregnant or lactating dogs, or dogs with cardiac disease. The most common adverse reactions were vomiting, diarrhea, decreased appetite, and lethargy. For full prescribing information see Galliprant package insert.

[1]Kirkby Shaw, K, et al. Vet Med Sci. 2016;2:3-9.
[2]Rausch-Derra L, et al. Am J Vet Intern Med. 2015;76(10):853-859.

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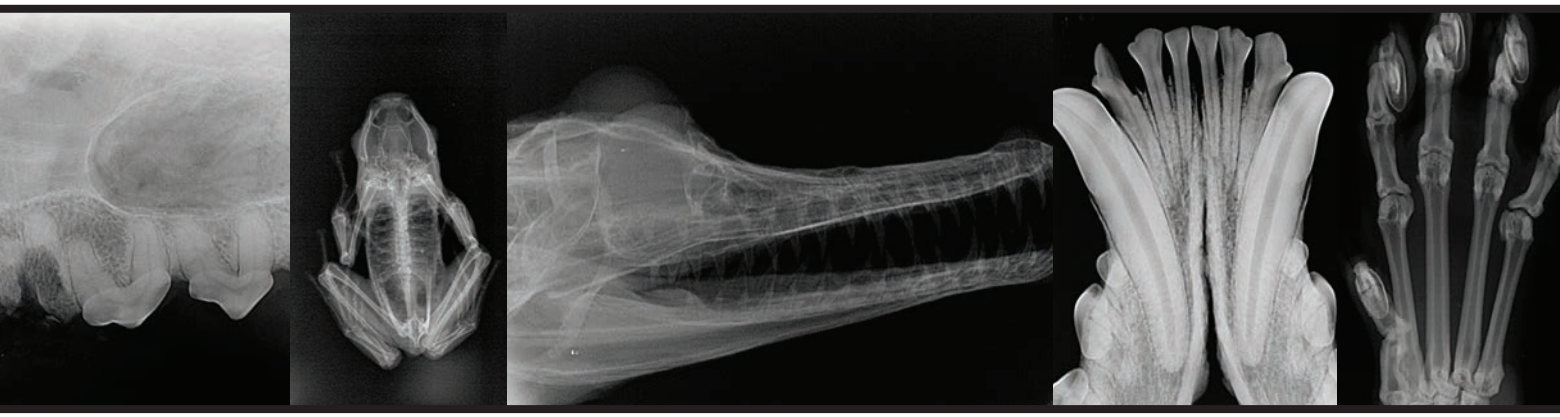

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Assessing Cats with Vehicular Trauma

Amanda Abelson, DVM, DACVAA, DACVECC
Cummings School of Veterinary Medicine
at Tufts University

In the literature

Lyons BM, Ateca LB, Otto CM. Clinicopathological abnormalities associated with increased animal triage trauma score in cats presenting for vehicular trauma: 75 cases (1998–2009). *J Vet Emerg Crit Care (San Antonio).* 2020;30(6):693-697.

FROM THE PAGE ...

Cats are commonly presented due to vehicular trauma. Rapid assessment is needed to provide appropriate emergency therapy and accurate prognosis. The animal trauma triage (ATT) score can be used to characterize disease severity and help predict outcome after traumatic insult. The ATT score is calculated based on physical examination abnormalities in 6 categories: perfusion, cardiac, respiratory, skeletal, neurologic, and eye/muscle/integument. The total ATT score ranges from 0 to 18, with higher values signifying greater severity of trauma, and can be performed by an experienced clinician or veterinary nurse. The ATT score has been validated in dogs and cats to demonstrate that for each 1-point increase, survival decreases 2.3 to 2.6 times[1]; in dogs, an ATT score of ≥5 has been associated with 83% sensitivity and 91% specificity in predicting nonsurvival.[2]

This retrospective study investigated whether a correlation exists between ATT and clinicopathologic alterations in cats presented following vehicular trauma. The study included 75 cats divided into 2 groups: cats with an ATT score ≥5 (n = 45) and cats with an ATT score <5 (n = 30). Differences in emergency point-of-care blood work (including packed cell volume [PCV], total protein, glucose, venous blood pH, plasma bicarbonate, base excess, venous partial pressure of carbon dioxide, plasma lactate, sodium, potassium, chloride, ionized calcium, ionized magnesium, BUN, and creatinine), Doppler blood pressure, and patient outcome were evaluated. Cats with an ATT score ≥5 had lower PCV, total plasma protein concentration, venous blood pH, base excess values, plasma bicarbonate concentrations, and Doppler blood pressure values, as well as higher glucose and lactate values. This group also had a higher mortality rate (57.8%) as compared with the second group (10%).

This study showed that the ATT score and emergency point-of-care blood work can be used to identify cats with more serious injury at the time of presentation. This may aid in providing appropriate therapy and determining prognosis.

... TO YOUR PATIENTS

Key pearls to put into practice:

1. The ATT score has been validated in both dogs and cats, is typically easy to determine because it is based on physical examination findings, and can be helpful in determining prognosis.
2. Cats with an ATT score ≥5 often have the following clinicopathologic changes as compared with cats that have an ATT score <5: lower PCV, total protein levels, blood pH, plasma bicarbonate concentration, base excess values, and Doppler blood pressure values, as well as higher blood glucose and lactate values.
3. Cats presented after vehicular trauma and that have an ATT score ≥5, or the blood work alterations listed directly above, should be suspected of having significant traumatic injury.

References

1. Rockar RA, Drobatz KS, Shofer FS. Development of a scoring system for the veterinary trauma patient. *J Vet Emerg Crit Care*. 1994;4(2):77-83.
2. Hall KE, Holowaychuck MK, Sharp CR, Reineke E. Multicenter prospective evaluation of dogs with trauma. *J Am Vet Med Assoc*. 2014;244(3):300-308.

revolution® PLUS
(selamectin and sarolaner topical solution)

Brief Summary: See package insert for full Prescribing Information.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: REVOLUTION PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*. REVOLUTION PLUS kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations, the treatment and control of tick infestations with *Ixodes scapularis* (black-legged tick), *Amblyomma maculatum* (Gulf Coast tick) and *Dermacentor variabilis* (American dog tick), the treatment and control of ear mite (*Otodectes cynotis*) infestations, and the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections for one month in cats and kittens 8 weeks and older, and weighing 2.8 pounds or greater.

CONTRAINDICATIONS: There are no known contraindications for the use of REVOLUTION PLUS.

WARNINGS: Human warnings: Not for human use. Keep this and all drugs out of the reach of children. In humans, REVOLUTION PLUS may be irritating to skin and eyes. REVOLUTION PLUS and selamectin topical solution contain isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Reactions such as hives, itching and skin redness have been reported in humans in rare instances after accidental dermal contact with selamectin topical solution. Individuals with known hypersensitivity to selamectin topical solution should use caution or consult a health care professional before applying this product on a cat. Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water; if wearing contact lenses, rinse the eyes first then remove contact lenses and continue to rinse for 5 – 10 minutes and seek medical attention. In case of ingestion by a human, contact a physician immediately. The safety data sheet (SDS) provides more detailed occupational safety information. For a copy of the SDS or to report a suspected adverse reaction, call Zoetis at 1-888-963-8471. Flammable - Keep away from heat, sparks, open flames or other sources of ignition.

PRECAUTIONS: Sarolaner, one of the ingredients in REVOLUTION PLUS, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Neurologic adverse reactions have been reported in cats receiving isoxazoline class drugs, even in cats without a history of neurologic disorders. Use with caution in cats with a history of neurologic disorders. The safe use of REVOLUTION PLUS has not been evaluated in kittens less than 8 weeks of age. The safe use of REVOLUTION PLUS has not been evaluated in breeding, pregnant, or lactating cats.

ADVERSE REACTIONS: In a field safety and effectiveness study, REVOLUTION PLUS was administered to cats with fleas. The study included a total of 430 cats (282 treated with REVOLUTION PLUS and 148 treated with imidacloprid + moxidectin once monthly for three treatments). Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions reported in the REVOLUTION PLUS group included those presented in the following table.

Adverse Reactions by Treatment Group

Adverse Reaction	REVOLUTION PLUS (*n* = 282)	Imidacloprid + moxidectin (*n* =148)
Lethargy	12 (4.3%)	1 (0.7%)
Skin lesions*	10 (3.5%)	3 (2.0%)
Anorexia	9 (3.2%)	3 (2.0%)
Pruritus	7 (2.5%)	3 (2.0%)
Conjunctivitis	7 (2.5%)	1 (0.7%)
Sneezing	6 (2.1%)	1 (0.7%)
Administration site hair changes (alopecia)	5 (1.8%)	0 (0.0%)
Administration site lesions (scabbing)	2 (0.7%)	0 (0.0%)

*Lesions not associated with application site.

In a second field safety and effectiveness study, REVOLUTION PLUS was administered to 124 cats with ear mites. Adverse reactions in cats treated with REVOLUTION PLUS included emesis, dermatitis and eczema, and pruritus. In a third field safety and effectiveness study, REVOLUTION PLUS was administered to 70 cats with hookworms. Adverse reactions in cats treated with REVOLUTION PLUS included diarrhea, anorexia, emesis, and lethargy. Foreign Market Experience: The following adverse events were reported voluntarily during post-approval use of the product in cats in foreign markets: ataxia, seizures, and tremors.

To report adverse reactions call Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

ANIMAL SAFETY: *Margin of Safety Studies*: One exploratory and two pivotal margin of safety studies were conducted with REVOLUTION PLUS. In the first study, REVOLUTION PLUS was applied topically to kittens eight weeks of age at doses of 12/2 (selamectin/sarolaner) mg/kg (1X), 36/6 mg/kg (3X), 45/7.5 mg/kg (3.75X), and 60/10 mg/kg (5X) every 28 days for eight consecutive doses. One female cat in the 3.75X group was found dead on study day 115. The cause was determined to be hemorrhage in multiple tissues secondary to a low platelet count. The role of the drug in contributing to this event is undetermined. No significant changes related to REVOLUTION PLUS were observed among the remaining cats for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry), gross pathology, histopathology or organ weights. In the second study, REVOLUTION PLUS was applied topically to cats 9 months of age at doses of 1X, 3X, and 5X every 28 days for six consecutive doses. Cosmetic changes at the application site occurred sporadically in all treatment groups and included wet appearance and dried white material. Hair loss at the dose site was also noted in two cats in the 1X group and one cat in the 5X group within 1-8 days after the fourth dose administered on day 84. No significant changes related to REVOLUTION PLUS were observed for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry). During an exploratory margin of safety study, one cat in the 60 mg/kg/10 mg/kg (selamectin/sarolaner) group (5X dose group) experienced piloerection, tremors, and mydriasis approximately 24 hours after receiving the third monthly dose of the combination. Signs resolved without treatment within 2 hours. This cat completed the study, receiving 3 subsequent 5X doses with no abnormal observations. *Oral safety study*: The safety of REVOLUTION PLUS administered orally to kittens was tested in case of accidental oral ingestion. Oral administration of the highest recommended topical dose of REVOLUTION PLUS to kittens resulted in transient lower food consumption and clinical findings of emesis, soft feces, and salivation. In one male, mild tremor was observed and resolved within 3 hours after dosing; the same cat demonstrated reduced activity approximately 6 hours after dosing. *Heartworm Positive Cat Safety of Selamectin*: Selamectin is the active ingredient in REVOLUTION PLUS that prevents heartworm disease in cats; it has been shown that the addition of sarolaner does not interfere with this activity. In a safety study in which selamectin topical solution was applied at 4 times the recommended dose to patent heartworm infected cats, no adverse reactions were observed. *Field safety:* In three well-controlled field studies, REVOLUTION PLUS was used concurrently with other medications, such as vaccines, cestocidal anthelmintics, antibacterials, sedatives, anesthetics, opioid analgesics, corticosteroids, and non-steroidal anti-inflammatories. No adverse reactions were associated with the concurrent use of REVOLUTION PLUS and other medications.

STORAGE CONDITIONS: Store at or below 30°C (86°F).

HOW SUPPLIED: Available in three separate dose strengths for cats of different weights (see **DOSAGE AND ADMINISTRATION**). REVOLUTION PLUS is available in cartons containing one, three, or six single dose tubes. The amount of liquid in tube varies for each weight range (2.8 - 5.5 lbs, 5.6 - 11 lbs, 11.1- 22 lbs). Tubes are never completely filled.

Approved by FDA under NADA 141-502 October 2018

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Distributed by: Zoetis, Kalamazoo, MI 49007

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revolution® PLUS
(selamectin and sarolaner topical solution)

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Application is QUICK AND EASY

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IMPORTANT SAFETY INFORMATION: The safe use of REVOLUTION PLUS has not been established in kittens less than 8 weeks old or in breeding, pregnant or lactating cats. Reported side eff ects in clinical trials included lethargy and anorexia. Use with caution in cats with a history of neurologic disorders. Sarolaner, one of the ingredients in REVOLUTION PLUS, is a member of the isoxazoline class, which has been associated with adverse reactions such as tremors, ataxia, and seizures. Reactions have occurred in cats with or without a history of neurologic disorders. In humans, REVOLUTION PLUS may be irritating to skin and eyes. **See Brief Summary of full Prescribing Information on page 46.**

REVOLUTION PLUS is an easy-to-apply, quick-drying, small-volume, monthly topical solution that protects against **fleas** (*Ctenocephalides felis*), **ticks** (**Black-legged** or **deer tick** [*Ixodes scapularis*], **Gulf Coast tick** [*Amblyomma maculatum*] and **American dog tick** [*Dermacentor variabilis*]), **ear mites** (*Otodectes cynotis*), **roundworms** (*Toxocara cati*), **hookworms** (*Ancylostoma tubaeforme*), and **heartworms** (*Dirofilaria immitis*) for cats and kittens as young as eight weeks of age and weighing 2.8 pounds or greater.

*REVOLUTION PLUS broadens the scope of protection for cats and kittens against fleas, ticks, ear mites, roundworms, hookworms, and heartworms.

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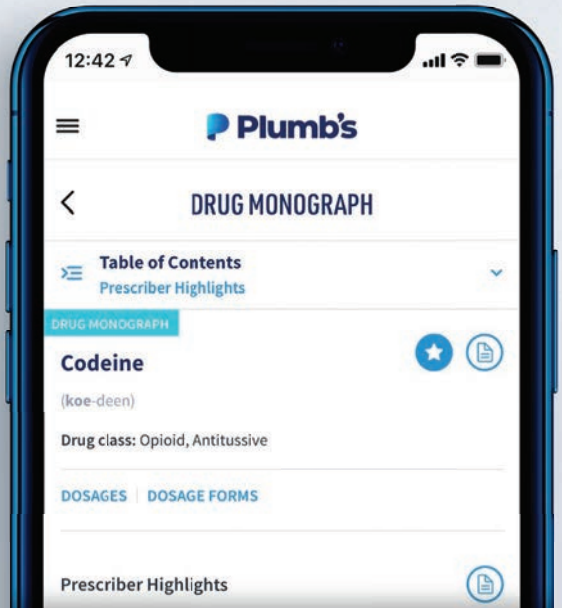

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Predicting Infection in Acute Traumatic Wounds

Jonathan Miller, DVM, MS, DACVS
Oradell Animal Hospital
Paramus, New Jersey

In the literature

Hamil LE, Smeak DD, Johnson VA, Dow SW. Pretreatment aerobic bacterial swab cultures to predict infection in acute open traumatic wounds: A prospective clinical study of 64 dogs. *Vet Surg*. 2020;49(5):914-922.

FROM THE PAGE ...

Infection development in wounds is common in veterinary patients. Predicting time of infection occurrence can assist in judicious antibiotic use. This study examined bacterial culture results in dogs with wounds caused by bites or other acute cutaneous trauma. Cultures were taken before and after wound lavage with lactated Ringer's solution.[1]

The primary objective of this study was to assess the type and quantity of bacteria present in the wound before and after lavage. The secondary objective was to evaluate whether culture results were useful for predicting ultimate wound infection. Size, type, and treatment of wounds by closure were examined in 64 dogs.

The rate of positive culture results significantly decreased from 76.6% before lavage to 56.3% after lavage, with an 86% reduction in the number of bacteria after irrigation. The species of bacteria grown in cultures were the same in 70.3% and different in 29.7% of wounds after lavage. Typical bacteria were *Staphylococcus* spp, *Streptococcus* spp, and *Pasteurella* spp. Although all dogs received a β-lactam antibiotic, 21.9% of wounds developed at least 1 sign of clinical infection during the 30-day follow-up. Postinfection cultures predominantly yielded *Staphylococcus spp*, *Escherichia coli*, and *Pseudomonas* spp, of which 69.2% were resistant to the prescribed prophylactic β-lactam antibiotic.

No relationship was found between development of clinical infection and prelavage culture, postlavage culture, number of bacteria cultured, or the wound size, type, or treatment. Although the reduction in bacteria after wound lavage was encouraging, the lack of reliable predictable factors for developing wound infection is a good reminder of the unpredictable nature of these cases.

... TO YOUR PATIENTS

Key pearls to put into practice:

1. Wound lavage with lactated Ringer's solution is effective for reducing bacterial load.
2. Cultures collected either before or after lavage do not appear to be helpful in predicting whether a wound will become infected or with which bacteria.
3. Resistance to prophylactic antibiotics is common in infected wounds.
4. Wound size, cause, and treatment after lavage do not seem to be useful in predicting infection.

Reference

1. Buffa EA, Lubbe AM, Verstraete FJ, Swaim SF. The effects of wound lavage solutions on canine fibroblasts: an in vitro study. *Vet Surg*. 1997;26(6):460-466.

Effects of Hetastarch on Colloid Osmotic Pressure

Amanda A. Cavanagh, DVM, DACVECC
Colorado State University

In the literature

Borrelli A, Maurella C, Lippi I, et al. Evaluation of the effects of hydroxyethyl starch (130/0.4) administration as a constant rate infusion on plasma colloid osmotic pressure in hypoalbuminemic dogs. *J Vet Emerg Crit Care*. 2020;30(5):550-557.

FROM THE PAGE ...

This study sought to investigate the effects of 2 CRIs of hydroxyethyl starch (HES) on plasma colloid osmotic pressure (COP) in dogs with hypoalbuminemia. A total of 24 dogs were included in the study. Dogs were randomly placed into 2 groups and given a synthetic colloid (HES 130/0.4, 1 mL/kg/hour CRI or 2 mL/kg/hour CRI for 24 hours). Causes of hypoalbuminemia varied and included diarrhea, chylothorax, protein-losing nephropathy, septic peritonitis, and hypoadrenocorticism. No difference was found in measured COP over time between the groups, and there was no discussion on the clinical effect of these infusions.

Intravascular hydrostatic pressure promotes fluid extravasation, and intravascular osmotic pressure opposes extravasation. COP (ie, oncotic pressure) is the portion of osmotic pressure attributed to plasma proteins (albumin accounts for ≈80% of COP)[1] and is dictated by the concentration of molecules in the solution, not the size of molecules. However, because colloids do not readily cross the vascular endothelium, due in part to size, these molecules increase COP by remaining in the intravascular space. Synthetic colloids are intravenous fluids manufactured with high molecular weight particles (eg, hetastarch, tetrastarch) that have the potential to increase COP and remain within the vascular space.

The modified Starling equation expresses the balance between osmotic and hydrostatic pressures governing fluid flux across the endothelium but does not represent all contributing factors to fluid movement. The endothelial glycocalyx (a meshwork of membrane-bound proteoglycans and glycoproteins lining the luminal surface of the endothelium[2]) is crucial to vascular integrity in health and disease. Soluble plasma molecules, including plasma proteins, dynamically integrate into and shed from the endothelial surface layer. Trauma, sepsis, and low protein environments, along with other pathologies, can rapidly lead to glycocalyx shedding.[3] Loss of the glycocalyx typically results in abnormal vascular permeability and fluid extravasation.[2,3] Synthetic colloids administered in the presence of a degraded glycocalyx can extravasate and accumulate in the interstitium; they do so more readily than natural colloids, eliminating the intended positive effect on COP.[3] Natural colloids (eg, albumin solutions, plasma transfusion) are more effective at restoring the glycocalyx.[3]

It is difficult to draw clinical conclusions from these study findings. Patients received variable volumes of concurrent crystalloid fluids that could have a dilutional effect on COP. Given their underlying diseases, these patients may have had an abnormal glycocalyx, leading to the loss of HES 130/0.4 molecules into the interstitium, with no net overall effect on COP. Because of the crucial role of the glycocalyx, measured COP is unlikely to predict the volume-expanding effects of a colloid. Although synthetic colloids are readily available, affordable, and can be stored safely, their use includes the risk for acute kidney injury, coagulopathy, and unfulfilled expectations of vascular expansion.[4-6]

… TO YOUR PATIENTS

Key pearls to put into practice:

1. Natural colloids (eg, canine albumin solution, plasma transfusion) can be considered in patients with hypoproteinemia that need fluid therapy and COP support.[7] Natural colloids are more effective at restoring the glycocalyx and vascular integrity.
2. Synthetic colloids should be used at the lowest effective dose for the shortest period of time possible. Prolonged use of synthetic colloids increases the risk for acute kidney injury in dogs.[4]
3. Synthetic colloids should not be used in patients with suspected or documented sepsis due to the risk for acute kidney injury; however, this originates from human guidelines and has not been proven in veterinary patients.

References

1. Smiley LE, Garvey MS. The use of hetastarch as adjunct therapy in 26 dogs with hypoalbuminemia: a phase two clinical trial. *J Vet Intern Med*. 1994;8(3):195-202.
2. Reitsma S, Slaaf DW, Vink H, van Zandvoort MAMJ, oude Egbrink MGA. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Arch*. 2007;454(3):345-359.
3. Milford EM, Reade MC. Resuscitation fluid choices to preserve the endothelial glycocalyx. *Crit Care*. 2019;23(1):77.
4. Sigrist NE, Kälin N, Dreyfus A. Changes in serum creatinine concentration and acute kidney injury (AKI) grade in dogs treated with hydroxyethyl starch 130/0.4 from 2013 to 2015. *J Vet Intern Med*. 2017;31(2):434-441.
5. Boyd CJ, Claus MA, Raisis AL, Hosgood G, Sharp CR, Smart L. Hypocoagulability and platelet dysfunction are exacerbated by synthetic colloids in a canine hemorrhagic shock model. *Front Vet Sci*. 2018;5:279.
6. Bae J, Soliman M, Kim H, et al. Rapid exacerbation of renal function after administration of hydroxyethyl starch in a dog. *J Vet Med Sci*. 2017;79(9):1591-1595.
7. Culler CA, Balakrishnan A, Yaxley PE, Guillaumin J. Clinical use of cryopoor plasma continuous rate infusion in critically ill, hypoalbuminemic dogs. *J Vet Emerg Crit Care* (*San Antonio*). 2019;29(3):314-320.

Research Note:
Homocysteine in Feline Chronic Kidney Disease

Although chronic kidney disease (CKD) is one of the most common diseases that affects elderly cats, few tests are currently recommended for diagnosing early-stage CKD and forecasting disease progression. In humans and dogs, homocysteine (Hcy) has been associated with certain aspects of renal dysfunction, including a positive correlation to systolic blood pressure in humans. Because it can be difficult to obtain blood pressure readings and to predict and track early renal disease in hospitalized cats, the authors investigated the potential applications of Hcy in feline CKD diagnostics. In this study, Hcy increases could be correlated to International Renal Interest Society (IRIS) stage; however, significant differences between IRIS groups were not always present. A significant difference was not found between concentration of Hcy and degree of proteinuria, and no correlation was found between high Hcy levels and hypertension. Thus, the authors concluded that serum creatinine provides more reliable information than Hcy concentration for purposes of early identification and staging of CKD in cats.

Source

Giraldi M, Paltrinieri S, Curcio C, Scarpa P. Serum concentration of homocysteine in spontaneous feline chronic kidney disease. *Vet J*. 2019;254:105358.

Research Note: **Vitamin D in Cats with Liver Disease**

Humans with chronic cholestatic liver disease (CLD) have deficiencies in vitamin D. Cats with inflammatory bowel disease, intestinal small cell lymphoma, and some infections have also been shown to be deficient in vitamin D. This prospective study compared vitamin D levels in cats with CLD with vitamin D levels in cats with nonhepatobiliary illness. Median serum vitamin D levels were similar between the groups, although low vitamin D occurred in a greater percentage of cats with CLD. Lower vitamin D was moderately correlated with higher WBC counts. Further study into the cause and clinical significance of these findings is warranted.

Source

Kibler L, Heinze CR, Webster CRL. Serum vitamin D status in sick cats with and without cholestatic liver disease. *J Feline Med Surg*. 2020;22(10):944-952.

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Otic gel
For Otic Use in Dogs Only

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

BRIEF SUMMARY (for full prescribing information, see package insert)

DESCRIPTION: OSURNIA contains 10 mg florfenicol, 10 mg terbinafine and 1 mg betamethasone acetate per mL and the inactive ingredients propylene carbonate, glycerol formal, hypromellose, phospholipid, oleic acid and BHT in an off-white to slightly yellow translucent gel.

INDICATION: OSURNIA is indicated for the treatment of otitis externa in dogs associated with susceptible strains of bacteria (*Staphylococcus pseudintermedius*) and yeast (*Malassezia pachydermatis*).

DOSAGE AND ADMINISTRATION: OSURNIA should be administered in the clinic. Clean and dry the external ear canal before administering the initial dose of the product. Administer one dose (1 tube) per affected ear(s) and repeat administration in 7 days. Do not clean the ear canal for 45 days after the initial administration to allow contact of the gel with the ear canal. Cleaning the ear may affect product effectiveness (see **Effectiveness** in the product insert). If alternative otic therapies are required it is recommended to clean the ear(s) before application. Open tube by twisting the soft tip. Insert the flexible tip into the affected external ear canal(s) and squeeze entire tube contents into the external ear canal(s). After application, gently massage the base of the ear to allow the gel to penetrate to the lower part of the ear canal.

CONTRAINDICATIONS: Do not use in dogs with known tympanic perforation (see **Precautions** in the product insert). Do not use in dogs with a hypersensitivity to florfenicol, terbinafine, or corticosteroids.

WARNINGS: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. In case of accidental skin contact, wash area thoroughly with water. Avoid contact to the eyes.

PRECAUTIONS: Do not administer orally. The use of OSURNIA in dogs with perforated tympanic membranes has not been evaluated. The integrity of the tympanic membrane should be confirmed before administering this product. Reevaluate the dog if hearing loss or signs of vestibular dysfunction are observed during treatment. Use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs (see **Animal Safety** in the product insert). Use with caution in dogs with impaired hepatic function (see **Animal Safety** and **Adverse Reactions** in the product insert). The safe use of OSURNIA in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

ADVERSE REACTIONS: The following adverse reactions were reported during the course of a US field study for treatment of otitis externa in dogs treated with OSURNIA with 1 tube per affected ear(s) and repeated after 7 days. The following adverse events are listed in decreasing order: elevated alkaline phosphatase, vomiting, elevated AST, ALT, ALP, weight loss (>10% body weight), and hearing decrease/loss. To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Dechra Veterinary Products at (866) 933-2472. 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.

EFFECTIVENESS: Effectiveness was evaluated in 235 dogs with otitis externa. The study was a double-masked field study with a placebo control (vehicle without the active ingredients). One hundred and fifty-nine dogs were treated with OSURNIA and seventy-six dogs were treated with the placebo control. All dogs were evaluated for safety. Treatment (1 mL) was administered to the affected ear(s) and repeated 7 days later. Prior to the first administration, the ear(s) were cleaned with saline but not prior to the Day 7 administration. Six clinical signs associated with otitis externa were evaluated: pain, erythema, exudate, swelling, odor and ulceration. Total clinical scores were assigned for a dog based on the severity of each clinical sign on Days 0, 7, 14, 30 and 45. Success was determined by clinical improvement at Day 45. The success rates of the two groups were significantly different (p=0.0094); 64.78% of dogs administered OSURNIA were successfully treated, compared to 43.42% of the dogs in the placebo control group.

STORAGE: OSURNIA should be stored under refrigerated conditions between 36° - 46° F (2° - 8° C). To facilitate comfort during administration, OSURNIA may be brought to room temperature and stored for up to three months.

MANUFACTURED FOR:
Dechra Veterinary Products
7015 College Boulevard, Suite 525
Overland Park, KS 66211 USA

Product of Great Britain

NADA # 141-437, Approved by FDA

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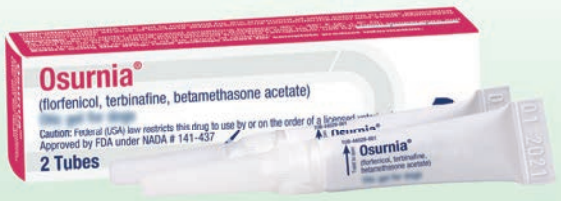
Two reasons to recheck.

1

2

Canine otitis externa treatment is only successful when you're confident your treatment is working. That's why the follow-up appointment is so important. Resolve the infection with 2-dose Osurnia, use the follow-up to monitor the response to treatment and trust the Dechra dermatology portfolio to help you manage the underlying problem.

To order or schedule a lunch and learn, call your Dechra representative or call (866) 683-0660.



Osurnia®
(florfenicol-terbinafine-betamethasone acetate)

For Veterinary Technical Support, Contact Dechra Veterinary Products at:
866-933-2472 | www.dechra-us.com | support@dechra.com

Important Safety Information
OSURNIA® (florfenicol/terbinafine/betamethasone acetate) is for otic use only under veterinary supervision. Do not use in dogs with known tympanic perforation or a hypersensitivity to florfenicol, terbinafine or corticosteroids. Adverse reactions observed during clinical trials include vomiting, increased liver enzymes and transient loss of hearing. Do not use in cats.

Osurnia is a registered trademark of Dechra Limited. Dechra is a registered trademark of Dechra Pharmaceuticals PLC. 00AD-OSU50215-1220

See page 52 for product information summary.

Anthropologic Insights on Companion Animal Antimicrobial Practices

Jeein Chung, DVM, MPH, DACVPM
Fairfax, Virginia

In the literature

Tompson AC, Chandler CIR, Mateus ALP, O'Neill DG, Chang Y-M, Brodbelt DC. What drives antimicrobial prescribing for companion animals? A mixed-methods study of UK veterinary clinics. *Prev Vet Med*. 2020;183:105117.

FROM THE PAGE ...

Antimicrobial resistance is a high-priority global health issue with significant relevance to veterinary medicine. Although companion animal clinicians routinely prescribe antibiotics, efforts to understand antimicrobial dispensation practices, as well as attitudes, behaviors, and institutional factors surrounding these practices, are poorly understood.

This study, which analyzed >460,000 antimicrobial dispensing events in dogs across the United Kingdom, provides a nonveterinary, anthropologic perspective that highlights knowledge and behaviors surrounding antimicrobial dispensation that can be taken for granted, breaking clinicians from isolated approaches of antibiotic treatment.

The study found that clinicians in the United Kingdom were unfamiliar with the term "Highest Priority Critically Important Antimicrobials" (HPCIAs), which is used by the World Health Organization to describe antimicrobials that are critically important in human medicine (including fluoroquinolones, quinolones, third-generation and higher cephalosporins, macrolides and ketolides, glycopeptides, and polymyxins).[1] In addition, although clinicians are commonly involved in dispensing antimicrobials, they may be less involved in the greater public health conversation.

The study noted a greater likelihood of prescribing HPCIAs (eg, cefovecin—a third-generation, long-acting cephalosporin) to small-breed dogs, as these dogs require a lower dose, which could be less cost-prohibitive. The study also noted that younger clinicians tended to champion prudent antibiotic use but did not feel they could challenge their colleagues, in part due to their relative position in the clinic.

Although the study included robust quantitative and qualitative methods and appropriate use of statistics, some inferences may not be meaningful in practice. For example, the study showed an increased odds ratio of administering HPCIAs to patients of increasing age. However, because these intervals were broken into ≈4-year age intervals (ie, <1.5 years of age, 1.5-4.3 years of age, 4.3-8.2 years of age, and >8.2 years of age), the study did little to signify associations between more meaningful age groups (eg, neonates, juveniles, seniors). The study also could not isolate attitudes and behaviors at the individual clinician level.

Important literature on antimicrobial practices in veterinary medicine (see ***Suggested Reading***) was included. It is important to review such literature for a better understanding of current antimicrobial practices to optimize use of HPCIAs in veterinary medicine.

… TO YOUR PATIENTS

Key pearls to put into practice:

1. HPCIA use should be reconsidered and limited in patients with routine infections, particularly in small-breed patients, in which a lower dosage and subsequent cost may seem beneficial.

2. Pet owner education regarding the ongoing public health issue of antimicrobial resistance, including consequences of uncontrolled and improper antibiotic use, is important. Any course of antibiotics should be taken in its entirety, and owners should be assisted (eg, via offering outpatient or at-home services) to ensure compliance when possible.

3. Clinicians should perform culture and susceptibility testing and recommend the most prudent antibiotic therapy for the patient and owner. Although it is up to the clinician to dispense antibiotics, when appropriate, owners should be given a range of antimicrobial therapeutic options so they can make fully informed decisions and maximize compliance.

Reference

1. World Health Organization. Highest priority critically important antimicrobials. WHO website. https://www.who.int/foodsafety/cia/en. Updated May 2019. Accessed January 2021.

Suggested Reading

Sarrazin S, Vandael F, Van Cleven A, De Graef E, de Rooster H, Dewulf J. The impact of antimicrobial use guidelines on prescription habits in fourteen Flemish small animal practices. *Vlaams Diergeneeskd Tijdschr*. 2017;86:173-182.

Weese JS. Investigation of antimicrobial use and the impact of antimicrobial use guidelines in a small animal veterinary teaching hospital: 1995-2004. *J Am Vet Med Assoc*. 2006;228(4):553-558.

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Research Note:

Diagnostic Value of Various Indexes in Psittacine Birds with Hepatic Disease

Liver disease is common in psittacine birds, but diagnosis can be challenging. Clinical signs are often nonspecific, and common serum indexes (eg, ALT, AST, ALP, lactate dehydrogenase, creatine phosphokinase) are not tissue-specific to the liver. This retrospective study evaluated the diagnostic value of plasma biochemistry, hematology, radiography, and endoscopic visualization of the liver in 28 pet birds with a diagnosis of liver disease based on histopathology. Investigators found that none of the antemortem diagnostics correlated with biopsy findings, and they concluded that liver biopsy is the best way to diagnose liver disease in psittacine birds, even if the liver is grossly normal.

Source

Hung CS, Sladakovic I, Divers SJ. Diagnostic value of plasma biochemistry, haematology, radiography and endoscopic visualisation for hepatic disease in psittacine birds. *Vet Rec*. 2020;186(17):563.

Liver biopsy is the best way to diagnose liver disease in psittacine birds, even if the liver is grossly normal.

Heartgard® Plus
(ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian. **INDICATIONS:** For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae *(Dirofilaria immitis)* for a month (30 days) after infection and for the treatment and control of ascarids *(Toxocara canis, Toxascaris leonina)* and hookworms *(Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense)*.

DOSAGE: HEARTGARD® Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older. For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food.The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids *(T. canis, T. leonina)* and hookworms *(A. caninum, U. stenocephala, A. braziliense)*. Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of D.immitis for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids *(T. canis, T. leonina)* and hookworms *(A. caninum, U. stenocephala, A. braziliense)*.

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.
In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. 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.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (see DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

Marketed by
Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

Made in U.S.A.

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Rev. 08-2018

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HEARTGARD® Plus (ivermectin/pyrantel) has tools available to help you educate your clients about the real risks of heartworm disease. With HEARTGARD Plus, you're recommending:

- ✔ Safe and trusted heartworm disease prevention that's still #1 after 33 years[1]
- ✔ The #1 dog-preferred, real-beef chew that makes compliance enjoyable for pets and pet owners[2]
- ✔ Highly effective control of five species of common intestinal parasites[3,4]
- ✔ Prevention backed by the HEARTGARD Plus Satisfaction Guarantee

Get clinic support at **HEARTGARDClinic.com**

IMPORTANT SAFETY INFORMATION: HEARTGARD® Plus (ivermectin/pyrantel) is well tolerated. All dogs should be tested for heartworm infection before starting a preventive program. Following the use of HEARTGARD Plus, digestive and neurological side effects have rarely been reported. For more information, please see full prescribing information or visit www.HEARTGARDClinic.com.

[1] Data on file at Boehringer Ingelheim. [2] Data on file at Boehringer Ingelheim. [3] Ascarid for Dog. Companion Animal Parasite Council. https://capcvet.org/guidelines/ascarid/. Accessed December 2, 2020. [4] Hookworms for Dog. Companion Animal Parasite Council. https://capcvet.org/guidelines/hookworms/. Accessed December 2, 2020.

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Boehringer Ingelheim

See page 56 for product information summary.

The Gentling Effect on Cats

Meghan E. Herron, DVM, DACVB
Gigi's Shelter for Dogs
Canal Winchester, Ohio

In the literature

Liu S, Paterson M, Camarri S, Murray L, Phillips CJC. The effects of the frequency and method of gentling on the behavior of cats in shelters. *J Vet Behav*. 2020;39:47-56.

FROM THE PAGE ...

Cats often show signs of stress when away from the home. Stress-reduction techniques have been evaluated in both hospitalized and shelter cat populations. Practical means of reducing stress are needed to promote positive welfare, accelerate healing, and, in the case of shelter cats, improve adoption appeal. *Gentling* has historically been used to describe a combination of friendly interactions between humans and animals and may include long body strokes, brief head patting, soft speaking, and resting a hand on the animal.

This study investigated how specific aspects and durations of gentling affected behavior in cats. Two experiments focused on the behavior of cats housed in a shelter in Queensland, Australia. In the first experiment, 60 cats were exposed to single-direction, head-to-tail petting for three 2-minute sessions per day, one 6-minute session per day, or no sessions. Cats were further divided into groups that experienced soft, friendly speaking delivered during the petting session or no vocalizations. The second experiment included 15 cats and more closely examined the duration of petting to determine whether 3-, 6-, or 9-minute sessions once daily for 4 days resulted in greater changes in behavior.

Results showed that a quiet petting session of 6 minutes once daily led to cats being near the front of their cage, being on the floor (rather than on a perch), and showing less pawing at the walls. Cats exposed to one 6- or 9-minute daily session showed an increase in purring, eating, and drinking. Soft speaking during the gentling sessions appeared to negate these positive effects.

Positive effects were noted only in the presence of the handler conducting the petting sessions. Cats did not remain on the floor or near the front of the cage when a stranger approached to pet them, suggesting familiarity plays a major role in cat comfort.

... TO YOUR PATIENTS

Key pearls to put into practice:

1. Although gentling may not dramatically alter behaviors of shelter cats, there is potential to improve cat's overall welfare and, therefore, overall health and well-being.
2. Hospitalized and boarded cats may benefit from a single 6- to 9-minute session of gentle petting per day, particularly if consistency of handlers is possible. When handling cats, keeping quiet appears to be more beneficial than using soft vocalizations.
3. Providing gentle handling and extended, purposeful interactions with cats may benefit patient welfare during hospitalization or boarding. This, in turn, may help cats engage in normal, healthy behaviors (eg, eating, drinking) and return to health more quickly.

Suggested Reading

Stella JL, Buffington CAT. Individual and environmental effects on health and welfare. In: Turner DC, Bateson P, eds. *The Domestic Cat: The Biology of Its Behavior*. 3rd ed. Cambridge University Press; 2014:185-200.

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Chlorhexidine can cause rare, but serious allergic reactions in humans. If you experience allergy symptoms, discontinue use immediately and seek medical treatment. Do not use DOUXO® S3 PYO Mousse in cats. Do not use DOUXO® S3 PYO Pads between the toes of cats.

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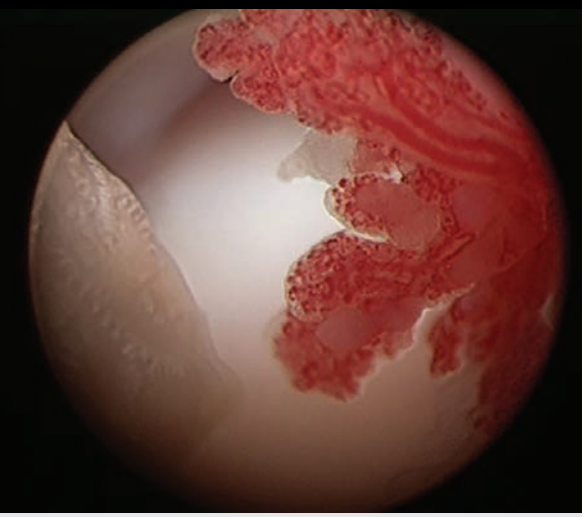
April 2021

clinicalnotes™

Breaking the Vicious Cycle of Inflammation in Canine Osteoarthritis

Steven M. Fox, MS, DVM, MBA, PhD
John M. Donecker, VMD, MS



▲ **FIGURE 1** Arthroscopic view of synovitis, characterized by infiltration of the synovial membrane with inflammatory cells resulting in angiogenesis and hyperplasia of the synovium

KEY POINTS

- Synovitis likely plays a pivotal role in the pathogenesis of OA, and a multimodal approach to managing OA may provide the best outcomes.
- Synovetin OA is a groundbreaking new treatment that provides durable relief from the chronic pain and inflammation of canine elbow OA. With 1 fast intra-articular injection, effects last up to 1 year, providing veterinarians and pet owners with a convenient approach to managing chronic pain and inflammation.

EXUBRION THERAPEUTICS

Synovetin OA

Osteoarthritis (OA) affects ≈20% of adult dogs[1] and is increasingly understood to be a vicious cycle. Recognizing this can open up new methods of treating this complex condition.[1]

OA has traditionally been viewed as a cartilage-only disease; however, synovitis (ie, inflammation of the synovium) is a common clinical finding.[2] Clinical signs of inflammation, histologic inflammation in osteoarthritic synovial tissue, and early cartilage lesions at the border of the inflamed synovium strongly indicate that synovitis plays a pivotal factor in the pathogenesis of OA.[3]

Synovial inflammation is implicated in many signs of OA, including joint swelling and effusion. The OA synovium has both inflammatory and destructive responses that depend largely on macrophages. These effects are cytokine-driven primarily through a combination of interleukin-1 and tumor-necrosing factor α.[4] Such observations are stimulating increased investigation into dynamic changes within the microenvironment of the synovial joint. The goal of this research is to develop therapies that can decrease both inflammatory synovitis and the production of degradative enzymes, which contribute significantly to the progression of OA.[4] With this goal in mind, a new focus for chronic pain management is the macrophage, which acts as the conductor of the inflammatory orchestra.

Inflammation, pain, impaired mobility and function, and structural changes characterize OA and contribute to its progression.[5-7] Pain is the hallmark of OA and results in both local and distant deterioration of the musculoskeletal system as a result of decreased and altered mobility. The pathologic process of OA, including joint capsule thickening and periosteal reactions, causes an altered range of motion, compounding musculoskeletal changes. Continual nociceptive input in the CNS results in somatosensory system deterioration and central sensitization with wind-up, amplifying the perception of pain.[8] Presently, the functional and structural changes associated with canine OA are incurable.

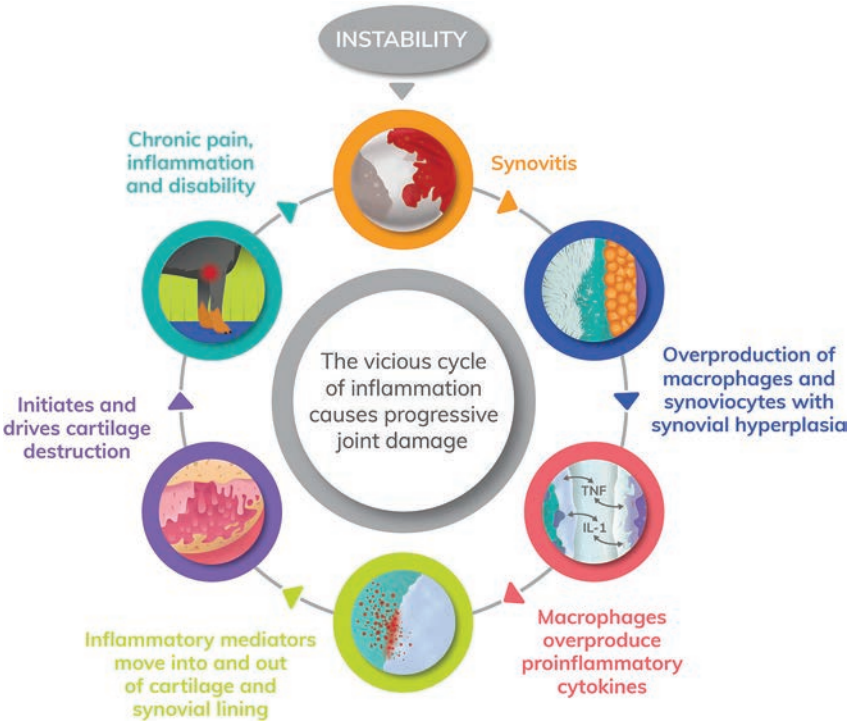
Early intervention has the greatest potential for providing the most effective management of OA by providing the opportunity to initiate an appropriate long-term care plan and to disrupt the progressive, vicious cycle of multidimensional deterioration involving both the neurologic and musculoskeletal systems.[9] From

such recognition has come a proposed instrument for staging canine OA, the Canine OsteoArthritis Staging Tool.[9] This tool can help identify OA at an early stage, noting preradiographic changes and improving dog owners' awareness of early-stage OA. Such clinician/pet owner synergism can help drive earlier and, therefore, more successful treatment by slowing disease progression.

Synovetin OA® is a groundbreaking new treatment that provides durable relief from the chronic pain and inflammation of canine elbow OA. With 1 fast intra-articular injection, effects last up to 1 full year, providing veterinarians and pet owners with a convenient approach to managing chronic pain and inflammation. By depleting proinflammatory macrophages (the source of chronic pain), Synovetin OA breaks the vicious cycle of inflammation, providing effective, long-lasting, safe, nonsystemic relief. During 3 separate year-long clinical trials involving 69 client-owned dogs, Synovetin OA was shown to be safe and effective.[10] One of these studies also showed Synovetin OA to be safe for re-administration to a previously treated elbow joint.

Radiosynoviorthesis (the restoration of the synovium using a radioisotope) is a well-established human procedure, having been used around the world for >60 years, and is associated with a low adverse event rate (≈0.013%).[11] Arthritic joints, which contain proinflammatory macrophages recruited during synovial hyperplasia, engulf colloid-embedded tin-117m microparticles, the active agent in Synovetin OA, and transport this complex to areas of synovial inflammation. Thereafter, tin-117m conversion electrons destroy the engorged macrophages responsible for inflammation via the noninflammatory process of apoptosis. This results in the synovium more closely reflecting the preinflammatory state and retards nociceptive transduction (pain). After decay, residual microparticles of inert tin are cleared via the lymphatic system to the liver.

Synovetin OA can be injected as an outpatient procedure. It is available from licensed specialty treatment centers, which can be located at **Synovetin.com**



▲ **FIGURE 2** The vicious cycle of inflammation. Overview of OA as a process rather than a disease, beginning with synovitis of a synovial joint caused by various sources, including trauma, instability, or idiopathic causes.[12-18] Regardless of etiology, histologic changes in the synovium include hyperplastic and hypertrophic synoviocyte changes and robust angiogenesis. Synoviocytes are mostly macrophages, and these changes cause an overproduction of proinflammatory cytokines (eg, matrix metalloproteinases, interleukins, tumor-necrosing factor α) that become part of the joint fluid milieu moving to and from synovial and cartilage tissues as the dog loads and unloads the joint. Matrix metalloproteinases, aggrecanases (metalloproteinases which cleave the aggrecan building blocks of cartilage), and nitric oxide, an important mediator in chondrocyte apoptosis, are particularly destructive to cartilage. With cartilage catabolism comes progressive inflammation, pain, and disability, contributing to the vicious cycle.

For references, please visit **cliniciansbrief.com/article/breaking-vicious-cycle-inflammation-canine-osteoarthritis**

For full prescribing information for Synovetin OA®, see next page.

Synovetin OA®

[Homogeneous Tin (^{117m}Sn) Colloid] Veterinary Device for Use in Dogs

NAME: Synovetin OA®

Tin (^{117m}Sn) stannic colloid in ammonium salt. It is supplied as a 2–4 mCi (74–148 MBq)/mL suspension for intra-articular (IA) injection.

NET QUANTITY

Vials contain a prescribed dose up to 6.0 mCi (222 MBq) at the date and time to treat one dog.

1 mL of suspension contains 2–4 mCi (74–148 MBq) of tin (^{117m}Sn) stannic colloid in ammonium salt at the date and time of end use.

PRODUCT DESCRIPTION

Synovetin OA® is a conversion electron therapeutic veterinary device comprising a colloidal, sterile suspension with a pH between 6.5 and 9.0 where at least 90% of the particles have a size between 1.5 µm and 20 µm (HORIBA light scatter instrument). The ^{117m}Sn emits monoenergetic conversion electrons (significant energies 127–158 keV; emission probability 113%) and imageable gamma radiation (159 keV, 86% abundant). Accompanying low-energy emissions are Auger electrons (<22 keV) and X-rays (<30 keV). The half-life of ^{117m}Sn is 14 days. ^{117m}Sn decays by isomeric transition to stable ^{117}Sn.

Excipients include ammonium carbonate ($(NH_4)_2CO_3$), ammonium chloride (NH_4Cl), ammonium iodide (NH_4I), and trace tin (Sn) salts.

MECHANISM OF ACTION

Synovetin OA® is a veterinary device consisting of a homogeneous tin colloid which emits discrete (<300 µm) low-energy conversion electrons confined to the joint space. The colloid is composed of microparticles (1.5 µm to 20 µm) that are retained in the joint space of the dog. The particles are absorbed and retained by synoviocytes and macrophages in the synovium, resulting in apoptosis and reduction of inflammatory cells. Elimination of the pro-inflammatory cells reduces inflammation of the joint synovium, thereby reducing pain associated with synovitis. The data, including radiographic evidence, supports use in Grade 1, 2, and 3 osteoarthritis (OA) of the elbow joint.

CAUTION

Federal law restricts this device to sale by or on the order of a licensed veterinarian trained in the use of radioactive veterinary medical products.

Use of this product is restricted to facilities with a compatible Radioactive Materials (RAM) license.

INTENDED USE

Synovetin OA® is intended to reduce synovitis and associated pain of canine elbow joints afflicted with osteoarthritis.

WARNINGS

Do not exceed 6.0 mCi (222 MBq) of radiation activity per dog per treatment. Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental injection or ingestion by humans.

PRECAUTIONS

Injection should be performed only by a licensed veterinarian skilled in the delivery of intra-articular (IA) injections who is located at a facility that has a RAM license.

Rigorous aseptic technique must be ensured during injection.

DIRECTIONS FOR USE

Use the chart below to determine the appropriate dose. Doses were determined using the elbow joint.

For example, a dog weighing 25 lbs. receives an IA dose of 0.9 mCi in each elbow to be treated.

Dog Weight (lbs.)	Synovetin OA® Dose per Elbow Joint (mCi)*
10–19 lbs.	0.6
20–29 lbs.	0.9
30–39 lbs.	1.2
40–49 lbs.	1.5
50–59 lbs.	1.7
60–69 lbs.	1.9
70–79 lbs.	2.2
80–89 lbs.	2.4
90–99 lbs.	2.6
100–109 lbs.	2.8
110 lbs. and over	3.0

***Dose will be limited to 3.0 mCi/elbow joint when weight exceeds 110 lbs., with the total body dose not exceeding 6.0 mCi (i.e., two elbow joints in 110-lb. or greater-sized dogs).**

PREPARATION FOR USE

Synovetin OA® is provided in a 3 mL glass vial within a lead cylinder. Each vial is for use with a single dog.

The product should be stored in the cardboard shipping container until needed for use. The **prescribed dose** should be **administered on the date noted** on the certificate accompanying the Synovetin OA®; however, it can be administered the day before or after if circumstances require injection on a different day. Always use proper personal protection equipment and precautions for handling radioactive medical products, including nitrile gloves, splash shield, safety goggles, back-fastening gowns, head covers, booties, and surgical masks.

STEP 1: When ready to withdraw the dose into a syringe and prior to removing the shrink wrap around the lead cylinder, gently **shake the lead cylinder for approximately 10 seconds to ensure proper mixing** of the product.

STEP 2: Remove the shrink wrap from the lead cylinder and dispose of it appropriately.

STEP 3: Remove the lead cylinder lid, but do not remove the glass vial from the lead cylinder.

STEP 4: Remove the colored flip cap from the vial and retain for placement on the vial after the dose is withdrawn.

STEP 5: Attach a plastic syringe (3 mL or other appropriate volume) to a 22-ga. needle. Where practical, use a syringe shield to maintain operator radiation doses as low as reasonably achievable and to meet existing license conditions.

STEP 6: While holding the container at an approximate 45° angle, insert the needle through the septum.

STEP 7: **Draw the prescribed volume into the syringe** for an individual elbow. **Under no circumstances should the volume be modified.** Repeat immediately for the second elbow dose. If both elbows are to be treated, both doses will be contained in a single vial. If there are any questions or concerns, contact Exubrion Therapeutics® Customer Service at 833-942-1247.

STEP 8: The dose should be resuspended by gently inverting the syringe if more than 10 minutes has elapsed since dose was drawn into the syringe.

STEP 9: Following use of Synovetin OA®, replace the colored flip cap on the vial, then place the lid on the lead container and secure the lid with tape. Mark the vial with a tentative disposal date 5 months from the present date. After 5 months, the vial should be measured with a handheld rate meter (GM detector) to verify that radioactivity has decayed. If the vial is less than or equivalent to background radiation, it can then be disposed of as regular trash. All waste disposals should be documented according to your radioactive materials license and federal or state regulations. Do not return the vial, any packaging components, or supplies to the manufacturer.

The shielded syringe or syringes and needles that are used for administration should be placed in shielded sharps containers for radionuclides of similar half-lives (two weeks) and disposed of according to local, state, and federal regulations.

ROUTE OF ADMINISTRATION

Intra-articular injection. The product must NOT be administered by any other route. Confirmation of needle placement is recommended, whether by anatomical landmarks, fluoroscope, C-arm, ultrasound, or radiography.

DIRECTIONS FOR ADMINISTRATION

Dogs should be appropriately anesthetized or sedated prior to administration. With the canine elbow positioned at 45 degrees of flexion, inject Synovetin OA® through a 22-ga. needle into the joint. This can be done between the lateral condyle of the humerus and the triceps tendon, but other approaches to the joint can be used. Following injection, gently flex and extend the treated joint through a range of motion to disperse the colloid throughout the joint compartments.

FREQUENCY OF ADMINISTRATION

If needed, Synovetin OA® can be readministered to a previously treated elbow at least 12 months after the last treatment.

DURATION OF EFFECT FROM ADMINISTRATION

Effectiveness has been shown to last up to 12 months following a single treatment of dogs with naturally occurring OA of the elbow.

MAXIMUM ANNUAL DOSE

Total radiation dose per joint should not exceed 3.0 mCi/joint, with the total body dose not exceeding 6.0 mCi (i.e., two elbow joints during a 12-month period).

ADVERSE REACTIONS

Dogs participating in clinical studies to evaluate safety and effectiveness (n=74 dogs, 97 elbow joints) exhibited no significant adverse reactions when administered Synovetin OA®. If adverse events are observed or suspected, please report them by calling Exubrion Therapeutics® Customer Service at 833-942-1247.

POST-INJECTION CARE

Following administration of Synovetin OA®, the dog can recover with other post-operation animals in the general clinic population. Once the dog has fully recovered, it can be discharged to go home with the approval of the facility radiation safety officer or authorized user. All treatment site policies and license requirements should be observed.

FACILITY CONTAMINATION ASSESSMENT

Removable radioactive contamination is assessed by using filter paper to wipe a known area (typically 100 cm^2), then count the number of interactions on the filter paper using a radiation detector with a known efficiency for counting the specific isotope in question. Empirical data using a Ludlum model 3 rate meter and 44-9 GM probe show the efficiency for ^{117m}Sn detection to be approximately 20% under 2D geometry. With a background rate of 100 counts per minute (cpm), this radiation detection system has a minimum detectable activity (MDA) of approximately 400 disintegrations per minute (dpm). The standard regulatory threshold for removable contamination in an unrestricted area is 2000 dpm for similar isotopes. Therefore, a Ludlum rate meter and GM is an adequate instrument to use for compliance measurements of removable contamination.

Note, ^{117m}Sn has a similar gamma emission as the commonly used medical radioisotope ^{99m}Tc along with several low-energy conversion electron emissions which would only aid in the detection efficiency of contamination.

EXPOSURE RATE MEASUREMENTS

Radioactive materials licenses require daily closeout surveys of all areas where unsealed radioactive material was used. These surveys can be completed with any rate meter capable of detecting the type of radiation emitted by the radioactivity. Further, license conditions require that release exposure rate measurements be completed prior to releasing animals who have been administered radioactivity. Most license conditions require the measurement taken not exceed 0.5 mR/h at 1 meter from the treatment site. The exposure rate release measurement and daily closeout surveys can be completed with either a standard volume ion chamber such as the Ludlum 9DP or Victoreen 451P, a Ludlum Model 3 rate meter and energy compensated GM probe 44-38, or a Ludlum 26-1 DOSE with energy flattening cover. While the ion chamber is the gold standard for exposure rate measurements, the Ludlum model 26-1 DOSE is the most practical because it can satisfy both contamination and exposure rate measurements (with dose flattening cover).

OWNER INSTRUCTIONS FOR POST-TREATMENT CARE

When the level of radiation is determined to be below the established levels for release, the dog can be discharged. The dog will, however, retain a low level of radioactivity in the treated joint(s) for a short period of time. There is no requirement for rehabilitation or restraint of the dog, and it can resume its normal level of activity. Specific written instructions based on the post-treatment radiation dosimetry for care and proximity to the treated dog will be provided by the radiation safety officer (RSO) or authorized user (AU) of a radioactive materials (RAM)-licensed veterinary hospital to the dog owner. A RAM-licensed veterinary hospital RSO or AU should contact Exubrion Therapeutics® if there are specific questions.

MANUFACTURED BY Theragenics Corporation for Exubrion Therapeutics®

Manufacturer's contact information:

Theragenics Corporation
5203 Bristol Industrial Way
Buford, GA 30518

Customer Service Phone: 833-942-1247

info@exubrion.com

STORAGE INSTRUCTIONS

Store in the shipping container at controlled room temperature (10°–30°C or 50°–86°F) until ready to use.

EXUBRION THERAPEUTICS

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July 2020 EXN-SYN-057

Survival of Dogs with Primary Lung Tumors

Christopher B. Thomson, DVM, DACVS (SA)
Veterinary Specialty Hospital of North County
San Marcos, California

In the literature

Rose RJ, Worley DR. A contemporary retrospective study of survival in dogs with primary lung tumors: 40 cases (2005-2017). *Front Vet Sci*. 2020;7:519703.

FROM THE PAGE ...

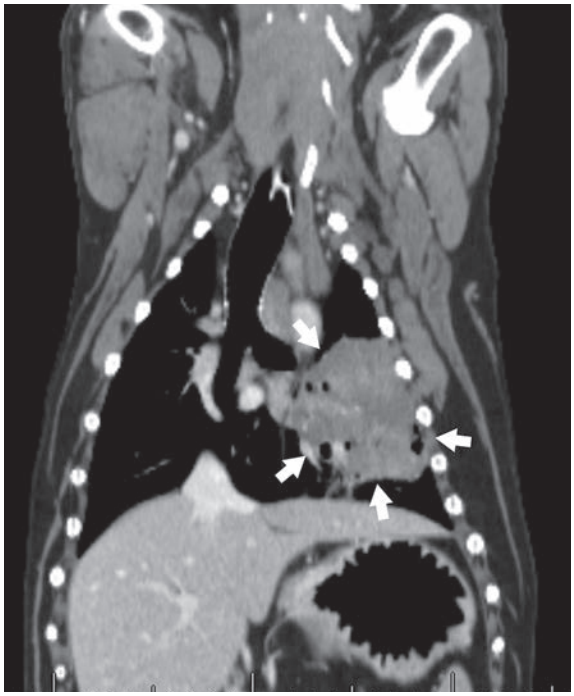
The prognosis for dogs diagnosed with primary pulmonary tumors depends on multiple factors, including clinical signs, tumor-specific factors (eg, size, histologic subtype, grade), and clinical stage.[1-4] Metastasis often occurs through the lymphatics because most lung tumors are derived from epithelial tissue; however, vascular and intra-airway spread has also been reported.[2,4] Historically, lymph node metastasis has been highly associated with a significantly shorter survival,[1-4] often prompting costly adjunctive treatment that may result in morbidity. Previous reports have suggested a survival of only 26 to 131 days in dogs with lymph node metastasis.[1-3,5]

In this contemporary retrospective study, records from 98 dogs that underwent surgery for a primary lung tumor were reviewed. Of these, 40 dogs with lymph node biopsy were also included. As this was a retrospective study, adjuvant treatments were not controlled. Multiple forms of maximally tolerated dose chemotherapy, metronomic chemotherapy, and other drugs were administered.

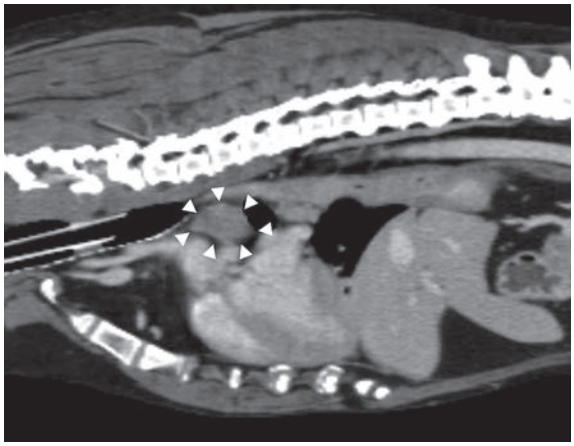
Of the dogs that underwent lymph node biopsy, 11 (27.5%) had metastasis to the lymph node. In univariate and multivariate analysis, presence of lymph node metastasis, administration of adjuvant chemotherapy, and mitotic index did not reach statistical significance. However, these data should be interpreted with caution due to the retrospective nature of the study and low numbers of cases in several categories. Similar to previous reports, the size of the primary tumor was negatively associated with survival; patients with a larger tumor had a significantly shorter survival time.

Lymph node metastasis was identified via surgical histopathology in some dogs that had radiologically normal lymph nodes per CT imaging. This highlights the importance of surgical lymph node extirpation when possible, despite anatomy being occasionally challenging and regardless of the preoperative imaging findings. Additional research regarding the long-term impact of lymph node metastasis in dogs with primary lung tumors is warranted.

Continued ▶



▲ **FIGURE 1** Dorsal reformatting of a contrast-enhanced CT scan in the soft tissue of a patient with a primary lung tumor. A large (>6 cm in diameter) primary lung carcinoma (***arrows***) causing lateral deviation of the mainstem bronchi can be seen.



▲ **FIGURE 2** Sagittal reconstruction of a CT scan (from the same patient in ***Figure 1***) that demonstrates an enlarged tracheobronchial lymph node (***arrowheads***)

… TO YOUR PATIENTS

Key pearls to put into practice:

1 Survival of dogs with primary lung tumors can be prolonged with surgery alone; median survival was 167 days in dogs with lymph node metastasis and 456 days in dogs without metastasis.

2 The size of the primary lung tumor significantly impacts survival; patients with smaller tumors have a prolonged median survival time.

3 Lymph node extirpation should be performed during surgery when possible, despite the occasional challenges with anatomy and regardless of the preoperative imaging findings.

References

1. Ogilvie GK, Haschek WM, Withrow SJ, et al. Classification of primary lung tumors in dogs: 210 cases (1975-1985). *J Am Vet Med Assoc*. 1989; 195(1):106-108.
2. McNiel EA, Ogilvie GK, Powers BE, Hutchison JM, Salman MD, Withrow SJ. Evaluation of prognostic factors for dogs with primary lung tumors: 67 cases (1985-1992). *J Am Vet Med Assoc*. 1997;211(11):1422-1427.
3. Polton GA, Brearley MJ, Powell SM, Burton CA. Impact of primary tumour stage on survival in dogs with solitary lung tumours. *J Small Anim Pract*. 2008;49(2):66-71.
4. Sabattini S, Mancini FR, Marconato L, et al. EGFR overexpression in canine primary lung cancer: pathogenetic implications and impact on survival. *Vet Comp Oncol*. 2014;12(3):237-248.
5. Paoloni MC, Adams WM, Dubielzig RR, Kurzman I, Vail DM, Hardie RJ. Comparison of results of computed tomography and radiography with histopathologic findings in tracheobronchial lymph nodes in dogs with primary lung tumors: 14 cases (1999-2002). *J Am Vet Med Assoc*. 2006;228(11):1718-1722.

STELFONTA®
(tigilanol tiglate injection)
1 mg/mL

SEEING IS BELIEVING

"Single-injection mast cell tumor destruction?

I didn't believe it, until I saw it myself."

Dr Melissa Wiest,
Veterinarian

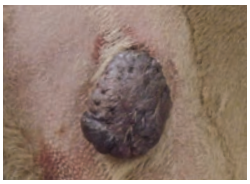
To place an order, contact your Virbac representative, or call 1-844-4-VIRBAC (1-844-484-7222).

To learn more, visit https://vet-us.virbac.com/stelfonta.

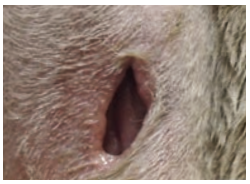
SCAN ME

STELFONTA® (tigilanol tiglate injection)

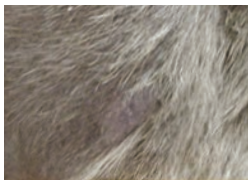
4 HOURS



7 DAYS



6 WEEKS



Hours: visible changes

Days: tumor destruction

Weeks: tumor site typically healed

IMPORTANT SAFETY INFORMATION

Accidental self-injection of STELFONTA® (tigilanol tiglate injection) may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary. In dogs, do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock. Formation of wounds, possibly extensive, is an intended and likely response to treatment with STELFONTA along with associated swelling, bruising and pain; these wounds are expected to heal. Appropriate pre- and post-treatment medications must be given, including a corticosteroid plus blocking agents for both H1 and H2 receptors, in order to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation. For full prescribing information, contact VIRBAC at 1-800-338-3659 or visit https://vet-us.virbac.com/stelfonta.

Please see full prescribing information on pages 66–67.

Virbac Shaping the future of animal health

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Virbac

STELFONTA®

(tigilanol tiglate injection)

1 mg/mL

For intratumoral injection in dogs only
Antineoplastic
Single use vial

WARNING: SEVERE WOUND FORMATION IN HUMANS; EXTENSIVE WOUND FORMATION, MAST CELL DEGRANULATION, AND DEATH IN DOGS DUE TO MAST CELL DEGRANULATION

Human Safety

- **Accidental self-injection of STELFONTA® may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary (see Dosage and Administration, Human Warnings and Adverse Reactions).**

Dog Safety

- **Always administer a corticosteroid (e.g. prednisone or prednisolone), an H1 receptor blocking agent (e.g. diphenhydramine), and an H2 receptor blocking agent (e.g. famotidine) when treating with STELFONTA to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation (see Contraindications and Dosage and Administration).**
- **Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see Contraindications, Warnings and Adverse Events).**
- **Treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds that require additional treatment and prolonged recovery times (see Warnings, Precautions and Adverse Events).**

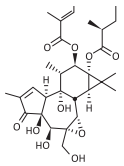
CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

The active ingredient for tigilanol tiglate injection is a phorbol ester that activates alpha, beta I, beta II, and gamma isoforms of protein kinase C. The chemical name is (4S,5S,6R,7S,8R,9R,10S,11R,12R,13S,14R)-12-(2E)-2-methylbut-2-enoatyl-13-[(2S)-2-methylbutyroyl]-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one. The molecular formula is $C_{30}H_{42}O_{10}$ and its molecular weight is 562.65 g mol^{-1}. Each mL of STELFONTA contains 1 mg tigilanol tiglate and sterile water for injection (60% v/v), propylene glycol (40% v/v), sodium acetate (<0.1% w/v), and glacial acetic acid (<0.1% w/v).

The chemical structure for tigilanol tiglate is:



INDICATION

STELFONTA injection is indicated for use in dogs for the treatment of:

- non-metastatic cutaneous mast cell tumors
- non-metastatic subcutaneous mast cell tumors located at or distal to the elbow or the hock

DOSAGE AND ADMINISTRATION

ALWAYS PROVIDE THE CLIENT INFORMATION SHEET TO THE DOG OWNER BEFORE DOSE ADMINISTRATION.

Concomitant medications

Administer the following medications to decrease the potential for severe systemic adverse reactions from mast cell degranulation:

- **Corticosteroid (e.g. oral prednisone or prednisolone at anti-inflammatory dose):** Start medication 2 days prior to STELFONTA treatment and continue for 8 days post-treatment (10 days total).
- **H1 receptor blocking agent (e.g. oral diphenhydramine):** Start medication on the day of STELFONTA treatment and continue for a total of 8 days.
- **H2 receptor blocking agent (e.g. oral famotidine):** Start medication on the day of STELFONTA treatment and continue for a total of 8 days.

Dosing Instructions

Administer STELFONTA as an intratumoral injection at a dose of 0.5 mL per cm^3 of tumor volume, as determined by the following calculations:

- **Determine the Tumor Volume in cm^3:**
  0.5 x [length (cm) x width (cm) x height (cm)]
- Confirm the Tumor Volume does not exceed 10 cm^3. Do not use STELFONTA if tumor volume is >10 cm^3.
- **Calculate the Dose Volume (mL) of STELFONTA to inject:**
  Tumor Volume x 0.5 mL
- Confirm the dose of STELFONTA does not exceed 0.25 mL/kg body weight.
- Do not exceed 5 mL per dog, regardless of tumor volume or body weight.
- The minimum dose of STELFONTA is 0.1 mL, regardless of tumor volume or body weight. If the calculated dose is <0.1 mL, administer 0.1 mL.

Administration of STELFONTA:

Sedation may be necessary to safely and accurately administer STELFONTA to decrease the chance of accidental self-injection. Wear gloves, eye protection, and lab coat or gown in the preparation and administration of STELFONTA. Care should be taken to restrict injections to the tumor only. STELFONTA should not be injected into the margins, beyond the periphery, or deep to the tumor.

- Shave the tumor site. Avoid manipulation of the tumor.
- Draw the calculated volume of STELFONTA into a sterile Luer-lock syringe with a 23 gauge needle.
- Identify an appropriate injection point on the edge of the tumor. See Figure 1. Insertion of the needle depends on the tumor's location, form, and appearance. If a tumor protrudes above the surface of the skin, insert the needle at an oblique angle of approximately 45°.
- Insert and embed the needle in the tumor through a single injection site and draw the syringe plunger back slightly to ensure STELFONTA is not injected into a blood vessel. While applying even pressure on the syringe plunger, move the needle back and forth in a fanning manner to inject STELFONTA into the tumor. See Figure 1. The drug should fully perfuse the entire tumor.
- When the total dose of STELFONTA has been administered, pause to allow tissue dispersion before removing the needle from the tumor. Pull back on the syringe plunger to create a small negative pressure before removing the needle to minimize leakage from the injection site.
- After the needle is withdrawn, apply light pressure for 30 seconds over the needle exit hole using a gloved finger. If leakage does occur, rinse injection site with saline to wash STELFONTA from the skin surface. Do not re-administer.
- To minimize risk of accidental self-injection, do not recap the needle. Dispose of the needle and syringe.

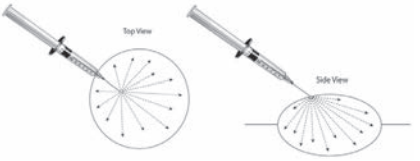


Figure 1: Dispersion of STELFONTA throughout the tumor.

CONTRAINDICATIONS

Do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock (e.g. on the body, head, or neck). This may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation (see **Adverse Reactions**).

WARNINGS

Human Safety

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

Caution is required during treatment to avoid accidental self-injection. Dogs undergoing treatment with STELFONTA should be adequately restrained and sedation used if necessary. Use a Luer-lock syringe to administer STELFONTA. Do not recap the needle. Accidental self-injection may result in local inflammatory reactions, including swelling, redness and severe wound formation. In case of accidental self-injection, immediately rinse the area with water, seek medical advice immediately, and show the package insert to the physician.

Wear personal protective equipment consisting of disposable gloves, protective eye wear, and a lab coat or gown when handling STELFONTA. STELFONTA is an irritant and accidental exposure to skin, eye, or by ingestion should be avoided. In case of dermal or ocular exposure, repeatedly wash the exposed skin or eye with water. If wearing contacts, rinse the eyes first then remove contacts and continue to rinse with water. If symptoms such as local signs of redness and swelling occur, or if there has been ingestion, seek the advice of a physician and show them the package insert.

Limited data is available on the potential teratogenic effects of STELFONTA. Therefore, STELFONTA should not be administered by women who are pregnant or planning to become pregnant.

People with known hypersensitivity to tigilanol tiglate or to any of the excipients should avoid contact with STELFONTA.

Animal Safety

Dogs should be monitored during and for 5-7 days after intratumoral treatment with STELFONTA for signs of systemic mast cell degranulation such as vomiting, diarrhea, lethargy, anorexia/hyporexia, altered breathing, hypotension, urticaria, edema at or away from the treated site, or bruising at or away from the treated site. If signs are observed, appropriate treatment should be started immediately.

Always administer the recommended concomitant medications (corticosteroids, H1, and H2 receptor blocking agents) with STELFONTA. Death has occurred following mast cell degranulation when these concomitant medications were not administered according to this Package Insert (see **Dosage and Administration** and **Adverse Reactions**).

STELFONTA can induce a substantial local inflammatory reaction which may result in pain, bruising, and swelling. During this time, an analgesic may be needed in addition to the use of corticosteroids and both H1 and H2 receptor blocking agents.

Treatment with STELFONTA causes tumor necrosis which is part of the mechanism of action of the drug. Bruising, heat, pain, and swelling may begin at the site within 2 hours of treatment. By day 7 after treatment, wound formation including full thickness dermal necrosis with exudate, peripheral tissue edema, erythema, skin discoloration, tissue sloughing, and necrotic eschar may occur.

In addition to tumor necrosis, treatment with STELFONTA has been associated with cellulitis and severe tissue sloughing extending away from the treated site resulting in extensive wounds (see **Adverse Reactions**).

Do not inject STELFONTA into normal subcutaneous tissue or adjacent tissues (e.g. beyond tumor margins) because severe edema, erythema and necrosis of the injected tissue may occur.

PRECAUTIONS

STELFONTA has not been evaluated in dogs with signs of systemic disease due to the mast cell tumor(s).

STELFONTA is not intended for the treatment of metastatic mast cell tumors.

The safe and effective use of STELFONTA has not been evaluated for simultaneous treatment of more than one mast cell tumor.

The safe and effective use of STELFONTA has not been evaluated in dogs with a mast cell tumor volume >10 cm^3.

Use STELFONTA with caution in tumors located within mucocutaneous regions (e.g., eyelids, vulva, prepuce, and anus) as tumor necrosis could cause a change in morphology of the mucocutaneous region resulting in loss of functional integrity.

Use STELFONTA with caution in mast cell tumors with significant ulceration as leakage of the drug from the ulcerated area may occur following treatment potentially reducing effectiveness.

The safe use of STELFONTA has not been evaluated in dogs with concurrent diseases that may result in delayed wound healing.

After treatment with STELFONTA, dogs may require additional care of the treated site to aid in the healing process. An Elizabethan collar or a non-constricting dry gauze bandage may be needed to prevent the dog from self-traumatizing the treated site.

After treatment with STELFONTA, separation from other household animals may be necessary to prevent grooming and trauma to the treated site.

The safe use of STELFONTA under conditions of use has not been evaluated in dogs younger than 3.5 years old.

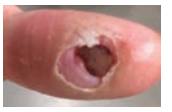
The safe use of STELFONTA has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

ADVERSE REACTIONS

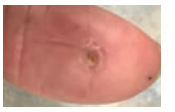
Human Exposure

There was one human exposure during the field study where the veterinarian had a needle stick injury to the thumb at completion of tumor treatment and was injected with an unknown amount of STELFONTA. The incident resulted in pain and necrosis of the center of the thumb at the point of needle stick. The wound healed over a period of three months. See Pictures 1 and 2 below. A separate needle stick injury was reported with a maximum potential dose of 0.1 mL tigilanol tiglate into the distal extremity of the left index finger, resulting in a localized burning sensation, local inflammation, bruising, muscular pain up the left arm, and localized tissue necrosis. Muscular pain resolved in the first 12-24 hours and the wound healed in 8 weeks. There have been other needle stick injuries reported, with at least one injection into a thumb, with minimal (stinging, pain, and swelling) to no adverse events associated with these accidental self-injections.

Picture 1. Thirteen days after self-injection



Picture 2. Seventy-four days after self-injection



Field Study

In a well-controlled, multi-center, randomized, double-masked field study evaluating the effectiveness and safety of STELFONTA for the treatment of cutaneous and subcutaneous mast cell tumors in dogs, 117 dogs treated with STELFONTA and 42 dogs receiving sham treatment (untreated control) were evaluated for safety. Eighty-one dogs were treated with STELFONTA on Day 0. Thirty-six previously untreated control dogs were treated with STELFONTA on Day 30. In addition, 18 dogs treated with STELFONTA on Day 0 had the same tumor re-treated with STELFONTA on Day 30 due to incomplete response. The most common adverse reactions included wound formation, injection site pain, lameness in the treated limb, vomiting, diarrhea, and hypoalbuminemia. Wound formation, vomiting, and diarrhea were mainly observed within the first 7 to 10 days after treatment. Injection site pain and lameness in the treated leg were mainly observed within the first 2 days after treatment. Hypoalbuminemia was mainly observed within the first 28 days after treatment. All dogs received concomitant medications as noted in the Effectiveness section. The adverse reactions during the study are summarized in Table 2 below.

Table 2: Adverse Reactions During the Field Study

Adverse Reaction	STELFONTA 1st Treatment (n = 117)	STELFONTA 2nd Treatment (n = 18)	UNTREATED CONTROL (n = 42)
Wound formation	110 (94.0%)	12 (66.7%)	3 (7.1%)
Injection site pain	61 (52.1%)	7 (38.9%)	1 (2.4%)
Lameness in treated limb	29 (24.8%)	2 (11.1%)	1 (2.4%)
Vomiting	24 (20.5%)	3 (16.7%)	4 (9.5%)
Diarrhea	24 (20.5%)	3 (16.7%)	2 (4.8%)
Hypoalbuminemia[a]	21 (18.0%)	2 (11.1%)	1 (2.4%)
Injection site bruising/ erythema/edema/ irritation	20 (17.1%)	3 (16.7%)	1 (2.4%)
Anorexia	14 (12.0%)	2 (11.1%)	3 (7.1%)
Regional lymph node swelling/enlargement	13 (11.1%)	1 (5.6%)	1 (2.4%)
Tachycardia	12 (10.3%)	0 (0.0%)	1 (2.4%)
Weight loss	12 (10.3%)	3 (16.7%)	5 (11.9%)
Cystitis	10 (8.6%)	1 (5.6%)	2 (4.8%)
Dermatitis	9 (7.7%)	1 (5.6%)	1 (2.4%)
Personality/behavior change	8 (6.8%)	0 (0.0%)	2 (4.8%)
Infection at injection site	8 (6.8%)	0 (0.0%)	0 (0.0%)
Tachypnea	7 (6.0%)	2 (11.1%)	1 (2.4%)
Pruritus	6 (5.1%)	3 (16.7%)	2 (4.8%)
Lethargy/Depression	6 (5.1%)	1 (5.6%)	1 (2.4%)
Pyrexia	3 (2.6%)	2 (11.1%)	0 (0.0%)

[a] There was a statistically significant decrease in albumin and albumin/globulin ratios at Day 7 in the STELFONTA group compared to the control group. The hypoalbuminemia ranged from 2.0 to 2.6 g/dL (reference range 2.7-3.9 g/dL).

Note: If an animal experienced the same adverse reaction more than once, only the highest grade was tabulated.

Adverse reactions were graded using the Veterinary Co-operative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE).[1] Most adverse reactions were Grade 1 (mild) or 2 (moderate). Grade 3 (severe) and 4 (life-threatening) adverse reactions in dogs treated with STELFONTA included: lameness in the treated limb (6 dogs), injection site pain (4 dogs), wound formation (3 dogs), lethargy/depression (3 dogs), anorexia (2 dogs), infection at injection site (1 dog), pruritis (1 dog), and tachycardia (1 dog).

Adverse reactions associated with use of the required concomitant corticosteroids were similarly reported in STELFONTA and untreated control dogs and included elevated alkaline phosphatase, polyuria, and polydipsia.

Wound Formation

Tumor observations were conducted at 2, 4, 8, and 24 hours and 4 days after treatment. The 81 dogs treated with STELFONTA on Day 0 were reported most frequently with swelling, bruising, pain and heat at all tumor observation timepoints. The following were reported at 24 hours post treatment:

- Swelling: 97.5% (79/81 dogs)
- Bruising: 91.4% (74/81 dogs)
- Pain: 69.1% (56/81 dogs)
- Heat: 53.1% (43/81 dogs)

At 24 hours post treatment, intact skin was reported in 71.6% (58/81 dogs) of STELFONTA® (tigilanol tiglate injection) treated dogs. On Day 4 intact skin was reported in 17.3% (14/81 dogs) of STELFONTA treated dogs. On Day 4, the following observations were reported with the highest frequency:

- Necrosis: 55.6% (45/81 dogs)
- Crater pockets: 37.0% (30/81 dogs)
- Exudate: 37.0% (30/81 dogs)
- Eschar: 28.4% (23/81 dogs)
- Ulceration: 11.1% (9/81 dogs)

A wound healing assessment was performed on the effectiveness dataset which included 80 dogs in the STELFONTA group and 38 dogs in the untreated control group. Wounds developed in 92.5% (74/80) of STELFONTA treated dogs and 2.6% (1/38) of untreated control dogs by Day 7. On Day 28, the presence of wounds was 40% (32/80) in the STELFONTA group and 2.6% (1/38) in the

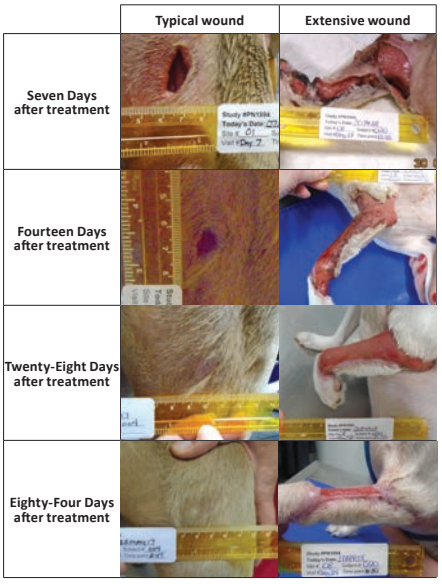
untreated control group. On Day 42 and Day 84, the presence of wounds was 27.1% (16/59) and 1.8% (1/57), respectively, in the STELFONTA group.

Exudate from the treated site including serous, serosanguinous, sanguineous, seropurulent, and purulent discharges were seen mainly on Day 7 and to a lesser extent on Day 14. Sloughing of the treated site was observed from Day 7 to Day 42, with decreasing frequency after Day 7. Peripheral pitting or non-pitting edema and erythema of the surrounding area were observed from Day 7 to Day 28, with decreasing intensity and frequency after Day 7. Necrotic eschar and epithelialization of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14. Granulation or hyper-granulation of the treated site was observed from Day 7 to Day 84, with decreasing frequency after Day 14.

The average wound size at Day 7 for a STELFONTA treated dog was 3.3 cm x 2.4 cm (original average tumor size 1.9 x 1.6 x 0.9 cm). On Day 28, the average wound size was 2.0 x 1.4 cm.

The largest total wound for a STELFONTA treated dog was reported seven days after treatment. The treated tumor was located on the left caudal stifle and the original tumor size measured 2.4 x 2.1 x 1.4 cm. The wound area initially consisted of three individual wounds recorded on the treated limb (both medial and lateral sides): 7.5 x 4.5 cm, 7.0 x 3.5 cm, and 11.5 x 7.0 cm. The wounds had reduced to 3.5 x 1.4 cm, 3.9 x 1.5 cm, and 9.7 x 4.3 cm 28 days after treatment, and 0.5 x 0.7 cm and 2.5 x 2.9 cm 42 days after treatment and were no longer present at 84 days after treatment.

One dog treated with STELFONTA was reported with an extensive wound formation (wound size 25.0 x 9.5 cm) with severe tissue slough (Grade 3) nine days after treatment of a mast cell tumor on the left metacarpal area (original tumor size 2.5 x 1.9 x 1.3 cm). The wound extended proximally up the leg to the shoulder and required bandaging of the leg and antibiotics. Scar contracture formed, requiring treatment under sedation to release the scar tissue. Clinical pathology abnormalities included elevated band neutrophils, anemia, and hypoalbuminemia. The wound had not fully healed by the end of the study 89 days after treatment. See pictures below comparing progression of this extensive wound formation versus commonly observed wound progression.



One dog treated with STELFONTA was reported with a bacterial infection and cellulitis in the right rear leg 9 days after treatment of a mast cell tumor on the right rear paw. There was bruising of the upper thigh and necrotic skin on the caudal right thigh and cranial aspect of the hock. Bloody discharge under the necrotic tissue revealed rod bacteria and toxic neutrophils. The dog was treated with intravenous fluids and antibiotics.

Systemic Mast Cell Degranulation and Death

Two dogs from two separate pilot studies died from a suspected mast cell degranulation reaction. Both dogs were treated with STELFONTA for a subcutaneous mast cell tumor located above the hock and did not receive the concomitant medications as prescribed.

In a pilot field study, one dog with a large (10 cm^3) subcutaneous mast cell tumor on the right hip was treated with STELFONTA. The dog had a partial Response Evaluation Criteria in Solid Tumors Guideline (RECIST)[2] response to the initial STELFONTA injection and was re-treated with STELFONTA, 30 days following the initial injection. The patient did not receive any of the recommended concomitant medications of prednisolone, chlorpheniramine and famotidine from 24 hours after the second STELFONTA injection. On Day 2 following the second STELFONTA injection, the dog became anorexic, painful, and lethargic and had marked swelling of the right hind limb extending to the chest with hemorrhagic, ruptured blisters near the hock joint. Blood work showed anemia, hypoproteinemia, liver enzyme elevations, and white blood cell changes (leukocytosis, neutrophilia, monocytosis, and thrombocytopenia). The dog was hospitalized, received a blood transfusion, and was administered intravenous fluids, prednisolone, chlorpheniramine and tramadol. Pitting edema progressed to the neck by four days following treatment. Despite supportive care, the dog died five days following treatment likely due to degranulation of the mast cell tumor and internal necrotic discharge of the tumor.

In a separate pilot field study, one dog with a moderate (2.53 cm^3) subcutaneous mast cell tumor on the left caudal hindlimb was treated with STELFONTA. The dog was treated with chlorpheniramine and meloxicam on treatment day (Day 0) and Day 1 only. The dog did not receive further concomitant medication. On Day 3 the dog was lethargic and there was significant edema at the injection site. While intravenous fluid and antibiotic therapy was initiated on Day 3, the dog rapidly deteriorated and died on the following day likely due to degranulation of the mast cell tumor. Pathology findings included widespread cellulitis, panniculitis (likely of bacterial origin), and septic peritonitis.

To report suspected adverse reactions, to obtain a Safety Data Sheet (SDS), or for technical assistance, call 800-338-3659. For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

INFORMATION FOR DOG OWNERS

Owners should be given the Client Information Sheet to read before STELFONTA is administered and should be advised to observe their dog for potential side effects, including signs of degranulation and excessive wound formation, as described in the sheet. Advise dog owners about possible adverse reactions, when to contact a veterinarian, and how to care for the treated tumor site.

Some discharge from the site following treatment is expected. The site can be cleaned with warm water as necessary. Advise owners to wear disposable gloves when cleaning the area.

CLINICAL PHARMACOLOGY

Mechanism of Action

In non-clinical pharmacology studies, tigilanol tiglate has been shown to have three inter-related effects that are responsible for its anti-tumor effectiveness. The first effect is to cause oncolysis of tumor cells that are in direct contact with tigilanol tiglate. The oncolysis occurs within the first hours following treatment and results from the disruption of mitochondrial functioning. Secondly, at the same time, tigilanol tiglate activates a protein kinase C (PKC) signaling cascade which propagates throughout the tumor, resulting in an acute inflammatory response with swelling and erythema extending to the tumor margins and immediate surroundings. This inflammatory response is normal and necessarily contributes to the activity of tigilanol tiglate by (a) restricting blood and oxygen supply to the tumor (causing localized hypoxia) and (b) recruiting and activating innate immune cells (principally neutrophils and macrophages), which then target the tumor and release reactive oxygen species, proteases, and cytokines that function in an antimicrobial role. This acute inflammatory response generally resolves within 48 to 96 hours. The third component of the antitumor activity of tigilanol tiglate is associated with direct effects of the drug in increased permeability of the tumor vasculature (via activation of the Beta-II isoform of PKC) leading to tumor vascular destruction. The resulting outcome is tumor destruction with a deficit or wound remaining where the tumor was located. Complete healing of the resulting wound following tumor destruction by STELFONTA is typically within 6 weeks.

Pharmacokinetics

Pharmacokinetic properties of STELFONTA were evaluated in a pilot study monitoring systemic levels following intratumoral injection, with a dose delivered according to the size of the mast cell tumor. A dose of 0.5 mg/cm^3 (0.5 mL/cm^3) was used in dogs with tumor volumes ranging from 0.1 to 6.8 cm^3 resulting in doses ranging from 0.002 mg/kg to 0.145 mg/kg and total doses ranging from 0.05 mg to 3.4 mg per dog. A total of 6 cutaneous and 5 subcutaneous mast cell tumors were treated in 10 dogs (one dog had two tumors treated consecutively). The following range of pharmacokinetic parameters were determined for STELFONTA in plasma: 1) elimination half-life ($t_{\frac{1}{2}}$): 2.85 to 36.87 hours; 2) maximum plasma concentration (C_{max}): 0.356 ng/mL to 13.8 ng/mL; and 3) area under the plasma concentration time-curve to the last quantifiable plasma concentration (AUC_{last}): 2.25 h*ng/mL to 31.24 h*ng/mL. There was no relationship between drug exposure (C_{max} and AUC_{last}) with tumor location (cutaneous or subcutaneous) or with total dose. In an evaluation of the pharmacokinetic data from the 5 dogs with cutaneous tumors, dose levels ranged from 0.002 mg/kg to 0.145 mg/kg. The highest C_{max} was 11.1 ng/mL and the highest AUC_{last} was 31.24 h*ng/mL at a dose of 0.125 mg/kg. For the other 5 dogs with subcutaneous tumors, doses ranged from 0.049 mg/kg to 0.094 mg/kg. The highest Cmax was 13.8 ng/mL and the highest AUC_{last} was 30.81 h*ng/mL at a dose of 0.094 mg/kg.

EFFECTIVENESS

The effectiveness of STELFONTA was evaluated in a well-controlled, multi-center, randomized, double-masked, field study in client-owned dogs. Enrolled dogs had non-metastatic World Health Organization stages Ia (one tumor confined to the dermis, without regional lymph node involvement) and IIIa (multiple dermal tumors; large infiltrating tumors without regional lymph node involvement) mast cell tumors that were (i) cutaneous, or (ii) subcutaneous and located at or distal to the elbow or the hock). A total of 123 client-owned dogs with a mast cell tumor measuring less than or equal to 10 cm^3 were randomized to treatment with a single injection of STELFONTA (n=81) or untreated control (n=42). On the day of treatment, the average tumor volume was 1.7 cm^3 (range 0.1 to 9.8 cm^3).

A total of 118 dogs were included in the effectiveness analysis; 80 dogs were in the STELFONTA group and 38 dogs were in the untreated control group. Response to treatment was evaluated using the RECIST[2], where complete response (CR) is resolution of the target tumor, partial response (PR) is at least a 30% decrease in the longest diameter of target tumor, stable disease (SD) is a decrease of less than 30% or increase of less than 20% of the longest diameter of the target tumor, and progressive disease (PD) is greater than a 20% increase in the longest diameter of the target tumor.

The primary effectiveness variable compared CR rates of the target tumor between groups 28 days after treatment. At 28 days after treatment, a statistically significantly greater proportion of dogs in the STELFONTA treated group (60/80; 75%) achieved CR compared to dogs in the untreated control group (2/38; 5.3%) (p<0.0001). An objective tumor response (CR + PR) was observed in 64/80 (80%) of the STELFONTA treated dogs. Of the 60 dogs in the STELFONTA group that experienced CR at Day 28, response assessment was conducted for 59 dogs at Day 42 and for 57 dogs at Day 84. At Day 42, 59/59 (100%) were disease-free at the injection site, and at Day 84, 55/57 (96%) were disease-free at the injection site.

For all dogs, corticosteroids (prednisone or prednisolone) were initiated 2 days prior to treatment at a dose of 0.5 mg/kg orally twice daily and continued for 7 days total (2 days before, on the day of treatment and 4 days after treatment), then 0.5 mg/kg once daily for an additional 3 days. An H1 receptor blocking agent (diphenhydramine [2 mg/kg orally twice daily]) and H2 receptor blocking agent (famotidine [0.5 mg/kg orally twice daily]) were initiated on the day of treatment and continued for 7 days.

Other medications prescribed based on veterinary discretion included antibiotics, analgesics, and sedatives. The majority of antibiotics were used to treat injection site infections. The majority of analgesics were used to treat tumor pain and were mainly initiated on the day of or day after treatment. Sedatives were used for treatment administration, conducting diagnostics, anxiety, and temperament issues.

Quality of Life (QoL)[3] was assessed by owners throughout the study and the mean scores for the QoL assessment was similar between the STELFONTA and untreated control groups at all time points.

Eighteen of the 20 STELFONTA treated dogs without CR received a second treatment. Twenty-eight days following the second treatment, CR was observed in 8/18 (44.4%) of these dogs. Forty-two days following the second treatment, CR was observed in 7/18 (38.9%) of treated dogs.

TARGET ANIMAL SAFETY

The margin of safety and toxicity of STELFONTA was evaluated in one laboratory safety study and one laboratory cardiovascular study utilizing final market formulation, and one pilot field study that used non-commercial formulation.

Laboratory Safety Study

In a 4-week laboratory safety study, 48 healthy Beagle dogs 6 to 8 months old were administered STELFONTA intravenously over a 15-minute infusion once a week for four weeks on Days 1, 8, 15, and 22, at doses of 0, 0.025, 0.05, or 0.075 mg/kg body weight (ranges between 0.02-0.036, 0.039-0.056, and 0.06-0.08 mg/kg, respectively due to dosing variability). Control dogs (0 mg/kg) received a vehicle control at a volume equal to the 0.075 mg/kg dose. The intravenous route was chosen for this study because subcutaneous injection was too toxic and intratumoral administration was not possible.

There were twelve dogs per group (6 male, 6 female). Four dogs/sex/group were necropsied two days following the last dose and two dogs/sex/group were necropsied following a 2-week recovery period.

All dogs survived the study, and there were no STELFONTA-related effects on body weight, body temperature, ophthalmic exam, electrocardiographic parameters, and organ weights.

The following were observed only in dogs in the groups administered STELFONTA: decreased food consumption from Days 22-29, vomiting/retching during infusion or immediately post-infusion, wound formation at the infusion site after the second or third dose, decrease in activity sporadically throughout the study, and elevations in alanine aminotransferase on Day 23.

The following were observed in all groups, including vehicle control and increased in a dose dependent manner: limited use of the leg that received the infusion occurred soon after dosing, weakness after the first dose, salivation and infusion site edema and erythema increased in frequency and severity throughout the study, and tremors occurred immediately post-infusion and increased in severity with dose.

Vomiting, retching, or tremors were typically transient and resolved within 1 hour of dosing while salivation also typically resolved within 4 hours.

Loose feces were observed in all groups in a non-dose dependent manner. Polydipsia occurred in the control, 0.05 and 0.075 mg/kg groups. Trending towards decreasing hematocrit (but still within reference intervals) was observed in all groups. One dog in the 0.05 mg/kg group was mildly anemic during recovery. Monocytosis and elevated fibrinogen were seen on Days 2 and 23 in a dose-dependent manner.

Gross pathology findings at the infusion site included inflammation, redness, and thickening of the skin. Correlative histopathology findings of the infusion site included hemorrhage, edema, inflammation, mixed cell infiltration, fibrosis, and chronic organizing thrombosis. Only one of the recovery dogs had changes at the infusion site consisting of proliferation of the intima. One dog in the 0.075 mg/kg group had a severe wound, confirmed on histopathology as ulcerative inflammation and severe necrosis with bacteria present. Gross pathology findings also included red, mottled, firm, and enlarged lymph nodes in all dose groups, including recovery dogs, confirmed on histopathology as inflammation, lymphoid hypercellularity, hemorrhage, and sinus histiocytosis. Pituitary cysts were observed in 7 dogs in all STELFONTA treated groups. One dog each from the 0.075 mg/kg group was observed to have kidney tubular vacuolation, dilation of the ventricles of the brain, and chronic inflammation of both the left thigh skeletal muscle and left sciatic nerve.

Laboratory Cardiovascular Study

In a 12-day laboratory cardiovascular study, 4 healthy male conscious telemeterized Beagle dogs approximately 2-4 years old were administered STELFONTA as a single intravenous infusion. Treatment consisted of four groups: vehicle control and STELFONTA at doses of 0.01, 0.025 and 0.075 mg/kg body weight. All four dogs received all treatments with at least a 3-day wash-out period.

All dogs survived the study and there were no STELFONTA-related effects on body temperatures, blood pressure, or electrocardiograms. The following were observed only after administration of STELFONTA in all dose groups: salivation, vocalization, incoordination, tremors, red feces, and decreased feces output. Retching, vomiting, incoordination, and changes in activity levels (increased and decreased) occurred in the 0.075 mg/kg group only. Tachycardia was seen for the first 2.5 hours after the 0.075 mg/kg dose only. The following were observed after administration of control or STELFONTA: excessive panting, decreased appetite, and limited usage/swelling of leg or paw. All dogs lost weight during the study. Clinical signs resolved around 4 hours post dosing.

Pilot Field Study

In a 28-day unmasked field study, 10 client-owned dogs, 6-14 years old were administered tigilanol tiglate (non-commercial formulation) once as an intratumoral injection at a dose of 0.5 mg tigilanol tiglate per cubic centimeter (cm^3) of tumor volume, not exceeding 0.25 mg/kg body weight (maximum dose of 5 mg). One dog was enrolled a second time to treat a second mast cell tumor after successful treatment of the first tumor. See pharmacokinetic results from this study under **Clinical Pharmacology**.

The most common observations after tigilanol tiglate administration were injection site reactions including necrosis, swelling (localized edema and edema extending well beyond the tumor injection site), pain, restlessness, inflammation, erythema, bleeding ulcerations, bruising/discoloration, sloughing of tissue, open wound, mild drainage, malodor, and presence of granulation tissue. Three dogs experienced dermatitis with or without skin necrosis in a region nearby but distinct from the tumor injection site. One dog experienced non-weight bearing lameness, muscle atrophy and enlarged popliteal lymph node. One dog vomited after administration. Three dogs required longer healing times beyond 28 days, with the longest requiring 5 months. Hypoalbuminemia was observed in 5 dogs with hypoproteinemia observed in 1 of these 5 dogs on Day 7 and was resolved by Day 28.

STORAGE INFORMATION

Store STELFONTA vials refrigerated at 2°C to 8°C (35°F to 46°F).

Do not freeze.

Keep the vial in the carton at all times to protect the vial from light.

For single use only.

Dispose of any unused product in accordance with disposal for routine medical waste.

HOW SUPPLIED

STELFONTA is supplied as a sterile, colorless liquid in a 5 mL clear, single-use glass vial containing 2 mL of STELFONTA at a concentration of 1 mg/mL tigilanol tiglate in sterile water for injection.

REFERENCES

1. Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.1. *Vet Compar Oncol.* 20 Jul 2011.
2. Eisenhauer EA, Therase P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1), *Eur J Cancer.* 2009; 45(2):228-247.
3. Lynch S, Savary-Bataille K, Leeuw B, Argyle DJ. Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer. *Vet Compar Oncol.* 2011; 9 (3):172-82.

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Prednisolone in the Development of Diabetes Mellitus in Cats

JD Foster, VMD, DACVIM
Friendship Hospital for Animals
Washington, D.C.

In the literature

Nerhagen S, Moberg HL, Boge GS, Glanemann B. Prednisolone-induced diabetes mellitus in the cat: a historical cohort. *J Feline Med Surg*. 2021; 23(2):175-180.

FROM THE PAGE ...

Most cats that develop diabetes mellitus (DM) are classified as having type 2 diabetes, which is caused by relatively impaired insulin secretion and insulin resistance.[1] Uncommonly, cats can develop DM secondary to hypercortisolemia, hypersomatotropism, or autoimmune destruction of the endocrine pancreas. Therefore, it is prudent to evaluate for the cause of insulin resistance in most cats with DM. Physical inactivity, previous steroid administration, male sex, and consumption of dry food have been shown to be risk factors for the development of DM.[2,3] However, the risk associated with prednisolone therapy on the development of DM is poorly described in the literature.

This retrospective study evaluated cats given prednisolone (≥1.9 mg/kg/day) for at least 3 weeks. The cats were monitored for at least 3 months after initial therapy. Of the 143 cats evaluated, 9.8% developed DM; most (85.7%) developed DM within the first 3 months of prednisolone therapy. No risk factors were observed to be associated with the development of DM in these cats; obesity and sex were not associated with increased risk. Although no significant difference was found among cats that did not develop DM, the median prednisolone dosage was higher in cats that did develop DM (3.5 mg/kg/day vs 2.9 mg/kg/day). This might be due to the small sample size of diabetic cats. In humans, steroid dosage is a risk factor for development of secondary DM[4]; larger studies in cats are required to evaluate this further. Lower dosages of prednisolone (≈5 mg/cat/day [NOT mg/kg]) are commonly used to treat inflammatory diseases (eg, inflammatory bowel disease, asthma). Anecdotally, DM has been observed in these patients; however, formal evaluation has not been done for lower dose or prolonged steroid administration, and until this has been evaluated, cats receiving any dosage of steroids should be considered to have increased risk for developing DM. Pet owners should be educated to monitor for clinical signs suggestive of disease.

Continued ▶

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PEA helps to support skin mast cells. In the presence of PEA, mast cells release less histamine and other inflammatory mediators, and skin health is maintained. In an 8-week study of 160 client-owned dogs, oral PEA-um was shown to be beneficial for skin health associated with seasonal allergies.[1]

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In a four-month double-blinded randomized controlled study of 57 client-owned cats, PEA-um was shown to have a significant effect on skin health. Owners also judged PEA-um to be superior to placebo in maintaining healthy skin. Tolerability was good, with only two cats experiencing non-serious side effects. The study authors concluded that PEA-um may be a valid option in the multimodal management of feline skin health.[2]

References: [1]Noli, C et al. Vet Dermatol. 2015; 26(6): 432-440. [2]Noli C et al. Vet. Dermatol. 2019; 30(5): 387-e117.

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… TO YOUR PATIENTS

Key pearls to put into practice:

1. Steroid therapy may result in insulin resistance and DM in cats. Most (64.3%) cats that developed DM in this study required insulin therapy and/or reduction of the steroid dosage for management of DM.
2. Although DM can occur at any time, most cats developed DM within the first 3 months of prednisolone therapy. It is important to educate owners on how to monitor for polyuria, polydipsia, and polyphagia, so cats that develop DM can be identified. Unlike dogs, cats do not normally exhibit polyuria/polydipsia with corticosteroid therapy.
3. Tapering to the lowest effective steroid dosage as soon as possible may help reduce the risk for secondary DM; however, this requires further evaluation.

References

1. Gilor C, Niessen SJM, Furrow E, DiBartola SP. What's in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. *J Vet Intern Med.* 2016;30(4):927-940.
2. McCann TM, Simpson KE, Shaw DJ, Butt JA, Gunn-Moore DA. Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. *J Feline Med Surg*. 2007;9(4):289-299.
3. Öhlund M, Egenvall A, Fall T, Hansson-Hamlin H, Röcklinsberg H, Holst BS. Environmental risk factors for diabetes mellitus in cats. *J Vet Intern Med*. 2017;31(1):29-35.
4. Suh S, Park MK. Glucocorticoid-induced diabetes mellitus: an important but overlooked problem. *Endocrinol Metab (Seoul)*. 2017;32(2):180-189.

CASE IN POINT ▸ CONTINUED FROM PAGE 86

References

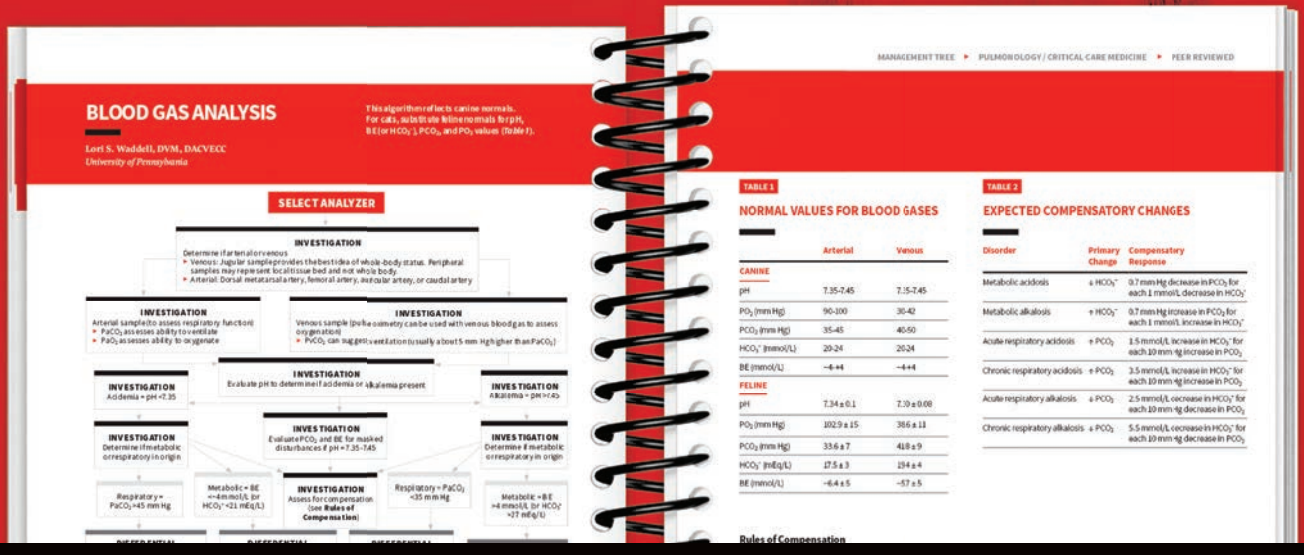
1. Kitaichi Y, Inoue T, Nakagawa S, et al. Sertraline increases extracellular levels not only of serotonin, but also of dopamine in the nucleus accumbens and striatum of rats. *Eur J Pharmacol*. 2010;647(103):90-96.
2. Friedman MJ, Marmar CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry*. 2007;68(5):711-720.
3. Brady K, Pearlstein T, Asnis GM. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000;283(14):1837-1844.
4. Davidson JRT. Remission in post-traumatic stress disorder (PTSD): effects of sertraline as assessed by the Davidson Trauma Scale, Clinical Global Impressions and the Clinician-Administered PTSD scale. *Int Clin Psychopharmacol*. 2004;19(2):85-87.
5. Pineda S, Anzola B, Ruso V, Ibáñez M, Olivares Á. Pharmacological therapy with a combination of alprazolam and fluoxetine and use of the trace element lithium gluconate for treating anxiety disorders and aggression in dogs. *J Vet Behav*. 2018;28:30-34.
6. Crowell-Davis SL, Seibert LM, Sung W, Parthasarathy V, Curtis TM. Use of clomipramine, alprazolam, and behavior modification for treatment of storm phobia in dogs. *J Am Vet Med Assoc*. 2003;222(6):744-748.
7. Beata C, Beaumon-Graff E, Diaz C, et al. Effects of alpha-casozepine (Zylkene) versus selegiline hydrochloride (Selgian, Anipryl) on anxiety disorders in dogs. *J Vet Behav*. 2007;2(5):175-183.
8. Levine ED, Ramos D, Mills DS. A prospective study of two self-help CD based desensitization and counter-conditioning programmes with the use of dog appeasing pheromone for the treatment of firework fears in dogs (*Canis familiaris*). *Appl Anim Behav Sci*. 2007;105(4):311-329.
9. Landsberg GM, Beck A, Lopez A, Deniaud M, Araujo JA, Milgram NW. Dog-appeasing pheromone collars reduce sound-induced fear and anxiety in beagle dogs: a placebo-controlled study. *Vet Rec*. 2015;177(10):260.
10. Denenberg S, Landsberg GM. Effects of dog-appeasing pheromones on anxiety and fear in puppies during training and on long-term socialization. *J Am Vet Med Assoc*. 2008;233(12):1874-1882.
11. Ley J, Kerr K, Seksel K. Results on the use of dog appeasement pheromone (DAP) collars in a selection of Australian dogs with anxiety disorders. *J Vet Behav*. 2010;5(1):45-46.
12. Burghardt WF. Preliminary evaluation of case series of military working dogs affected with canine post-traumatic stress disorder (N = 14). In: Proceedings from the American College of Veterinary Behaviorists-American Veterinary Society of Animal Behavior Veterinary Behavior Symposium; July 19, 2013; Chicago, IL.

Suggested Reading

FAS spectrum and pain algorithm. Fear Free website. https://fearfreepets.com/fas-spectrum. Accessed November 2020.

clinician's brief

SCRATCHING YOUR HEAD OVER THE LATEST TEST RESULTS?



BLOOD GAS ANALYSIS

This algorithm reflects canine normals. For cats, substitute feline normals for pH, BE (or HCO_3^-), PCO_2, and PO_2 values (*Table 1*).

Lori S. Waddell, DVM, DACVECC
University of Pennsylvania

SELECT ANALYZER

INVESTIGATION
Determine if arterial or venous
- Venous: Jugular sample provides the best index of whole-body status. Peripheral samples may represent local tissue bed and not whole body.
- Arterial: Dorsal metatarsal artery, femoral artery, auricular artery, or caudal artery

INVESTIGATION
Arterial sample (to assess respiratory function)
- $PaCO_2$ assesses ability to ventilate
- PaO_2 assesses ability to oxygenate

INVESTIGATION
Venous sample (pulse oximetry can be used with venous blood gas to assess oxygenation)
- $PvCO_2$ can suggest ventilation (usually about 5 mm Hg higher than $PaCO_2$)

INVESTIGATION
Evaluate pH to determine if acidemia or alkalemia present

INVESTIGATION
Acidemia = pH <7.35

INVESTIGATION
Alkalemia = pH >7.45

INVESTIGATION
Determine if metabolic or respiratory in origin

INVESTIGATION
Evaluate PCO_2 and BE for masked disturbances if pH = 7.35-7.45

INVESTIGATION
Determine if metabolic or respiratory in origin

Respiratory = $PaCO_2$ >45 mm Hg

Metabolic = BE >−4 mmol/L (or HCO_3^- <21 mEq/L)

INVESTIGATION
Assess for compensation (see **Rules of Compensation**)

Respiratory = $PaCO_2$ <35 mm Hg

Metabolic = BE >4 mmol/L (or HCO_3^- >27 mEq/L)

MANAGEMENT TREE ▸ PULMONOLOGY / CRITICAL CARE MEDICINE ▸ PEER REVIEWED

TABLE 1
NORMAL VALUES FOR BLOOD GASES

	Arterial	Venous
CANINE		
pH	7.35-7.45	7.35-7.45
PO_2 (mm Hg)	90-100	30-42
PCO_2 (mm Hg)	35-45	40-50
HCO_3^- (mmol/L)	20-24	20-24
BE (mmol/L)	−4-+4	−4-+4
FELINE		
pH	7.34 ± 0.1	7.30 ± 0.08
PO_2 (mm Hg)	102.9 ± 15	38.6 ± 11
PCO_2 (mm Hg)	33.6 ± 7	41.8 ± 9
HCO_3^- (mEq/L)	17.5 ± 3	19.4 ± 4
BE (mmol/L)	−6.4 ± 5	−5.7 ± 5

TABLE 2
EXPECTED COMPENSATORY CHANGES

Disorder	Primary Change	Compensatory Response
Metabolic acidosis	↓ HCO_3^-	0.7 mm Hg decrease in PCO_2 for each 1 mmol/L decrease in HCO_3^-
Metabolic alkalosis	↑ HCO_3^-	0.7 mm Hg increase in PCO_2 for each 1 mmol/L increase in HCO_3^-
Acute respiratory acidosis	↑ PCO_2	1.5 mmol/L increase in HCO_3^- for each 10 mm Hg increase in PCO_2
Chronic respiratory acidosis	↑ PCO_2	3.5 mmol/L increase in HCO_3^- for each 10 mm Hg increase in PCO_2
Acute respiratory alkalosis	↓ PCO_2	2.5 mmol/L decrease in HCO_3^- for each 10 mm Hg decrease in PCO_2
Chronic respiratory alkalosis	↓ PCO_2	5.5 mmol/L decrease in HCO_3^- for each 10 mm Hg decrease in PCO_2

Rules of Compensation

Reach for the guidance of 100+ easy-to-follow management trees from *Clinician's Brief*.

Created by a team of veterinary experts, the *Clinician's Brief* Algorithm Collection offers roadmaps for a wide range of cases, from common cardiac arrhythmias to refractory dermatophytosis.

Order your guide to hundreds of clinical presentations at cliniciansbrief.com/algorithms

Experience the many layers of Advantage Multi®
(imidacloprid+moxidectin)

*Roundworms, hookworms and whipworms in dogs and roundworms and hookworms in cats.

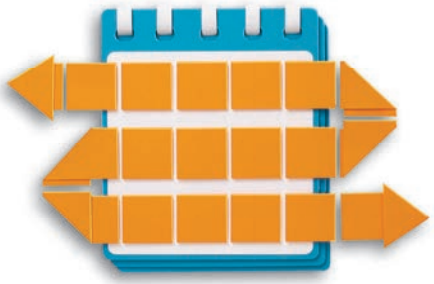
CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

One monthly dose, multiple parasites

Two layers of heartworm coverage

Backward protection

Clears tissue stages of heartworms acquired during the previous month.



Forward protection*

Keeps killing newly acquired heartworm larvae all day, every day, all month long.[1,2]

Fleas don't have to bite to die

Works through contact to paralyze and kill parasites

Stops biting fleas within 3-5 minutes.[†3-5]

No biting necessary, unlike oral preventives

Oral preventives work through the bloodstream, requiring fleas to bite and drink blood to die.

Treats and controls intestinal worms

Kills multiple parasites

Roundworms, hookworms and whipworms in dogs and roundworms and hookworms in cats.

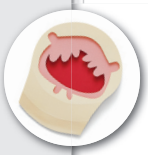
Covers multiple parasite life stages

Most products only cover adult worms.[††]

*Forward protection from heartworm infection means that after a single dose of Advantage Multi®, blood levels of moxidectin are continuously at or above the concentration required to kill newly acquired heartworm larvae and are maintained between continued monthly administration of these products.

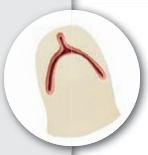
†Three in vivo experiments were conducted to evaluate the effect of Advantage® Topical Solution (imidacloprid) on fleas (*Ctenocephalides felis*). A total of seven (7) dogs were treated with Advantage® Topical Solution. Seven (7) days after application, areas on the dogs were shaved to allow visual observation. A petri dish was attached over each spot and then infested with up to 100 fleas. In all replicates, the fleas stopped their feeding activity and started tetanic trembling movements within 3-5 minutes. In one hour, all fleas were dead.[3-5]

††Based on label comparisons.



Hookworms

	advantage multi® for dogs (imidacloprid+moxidectin)	Heartgard® Plus	ProHeart® 12
A. caninum L4	✔		✔*
A. caninum immature adults	✔		
A. caninum adults	✔	✔	✔*
A. braziliense		✔	
U. stenocephala L4	✔		✔*
U. stenocephala immature adults	✔		
U. stenocephala adults	✔	✔	✔*



Roundworms

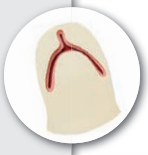
T. canis L4	✔		
T. canis adults	✔	✔	
T. leonina	✔	✔	

Whipworms

T. vulpis	✔		

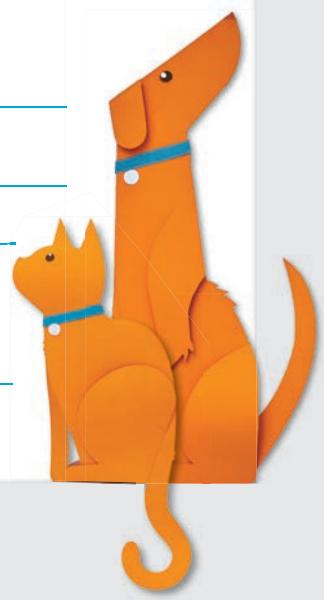
Hookworms

	advantage multi® for cats (imidacloprid+moxidectin)	Revolution®	Revolution® Plus
A. tubaeforme L4	✔		
A. tubaeforme immature adults	✔		
A. tubaeforme adults	✔	✔	✔



Roundworms

T. cati L4	✔		
T. cati adults	✔	✔	✔



Based on label comparisons for intestinal parasites.

*ProHeart® 12 is indicated for the treatment of existing larval and adult hookworm (*Ancylostoma caninum* and *Uncinaria stenocephala*) infections at time of injection.

Dogs: WARNING: **DO NOT ADMINISTER THIS PRODUCT ORALLY.** For the first 30 minutes after application, ensure that dogs cannot lick the product from application sites on themselves or other treated animals. Children should not come in contact with the application sites for two (2) hours after application. (See Contraindications, Warnings, Human Warnings and Adverse Reactions for more information.) Cats: Do not use on sick, debilitated, or underweight cats. Avoid oral ingestion.

Protect your patients from heartworms, fleas and IPs with the many layers of Advantage Multi®

(imidacloprid + moxidectin)

To experience multi-layered protection, contact your Elanco sales representative.

[1] Bowman DD, Ohmes CM, Hostetler JA, et al. Efficacy of 10% imidacloprid + 2.5% moxidectin topical solution (Advantage Multi® for Dogs) for the prevention of heartworm disease and infection all month long. Parasite Vector. 2017;10(2):59-64.

[2] Elanco Animal Health. Data on file.

[3] Mehlhorn H, Hansen O, Mencke N. Comparative study on the effects of three insecticides (fipronil, imidacloprid, selamectin) on developmental stages of the cat flea (Ctenocephalides felis Bouché 1835): a light and electron microscopic analysis of in vivo and in vitro experiments. Parasitol Res. 2001;87(3):198-207.

[4] Mehlhorn H. Mode of action of imidacloprid and comparison with other insecticides (i.e., fipronil and selamectin) during in vivo and in vitro experiments. Suppl Compend Contin Educ Pract Vet. 2000;22(4A):4-8.

[5] Mehlhorn H, Mencke N, Hansen O. Effects of imidacloprid on adult and larval stages of the flea Ctenocephalides felis after in vivo and in vitro applications: a light- and electron-microscopy study. Parasitol Res. 1999;85(8-9):625-637.

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Elanco

Advantage Multi® for Dogs and for Cats
(imidacloprid + moxidectin)

BRIEF SUMMARY: Before using *Advantage Multi® for Dogs* (imidacloprid+moxidectin) or *Advantage Multi® for Cats* (imidacloprid +moxidectin), please consult the product insert, a summary of which follows:

CAUTION: Federal (U.S.A.) Law restricts this drug to use by or on the order of a licensed veterinarian.

Advantage Multi for Dogs:

WARNING

- **DO NOT ADMINISTER THIS PRODUCT ORALLY.**
- **For the first 30 minutes after application ensure that dogs cannot lick the product from application sites on themselves or other treated animals.**
- **Children should not come in contact with the application sites for two (2) hours after application.**

(See Contraindications, Warnings, Human Warnings, and Adverse Reactions for more information.)

INDICATIONS:

Advantage Multi for Dogs is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and the treatment of *Dirofilaria immitis* circulating microfilariae in heartworm-positive dogs. *Advantage Multi for Dogs* kills adult fleas and is indicated for the treatment of flea infestations *(Ctenocephalides felis). Advantage Multi for Dogs* is indicated for the treatment and control *of sarcoptic mange* caused by *Sarcoptes scabiei var.canis. Advantage Multi for Dogs* is also indicated for the treatment and control of the following intestinal parasites species: Hookworms *(Ancylostoma caninum) (Uncinaria stenocephala)*, Roundworms *(Toxocara canis)* (*Toxascaris leonina) and* Whipworms (*Trichuris vulpis)*.

Advantage Multi for Cats is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis. Advantage Multi for Cats* kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations. *Advantage Multi for Cats* is also indicated for the treatment and control of ear mite *(Otodectes cynotis)* infestations and the intestinal parasites species Hookworm *(Ancylostoma tubaeforme)* and Roundworm *(Toxocara cati)*. **Ferrets:** *Advantage Multi for Cats* is indicated for the prevention of heartworm disease in ferrets caused by *Dirofilaria immitis. Advantage Multi for Cats* kills adult fleas *(Ctenocephalides felis)* and is indicated for the treatment of flea infestations in ferrets.

CONTRAINDICATIONS: Do not administer this product orally. (See WARNINGS). Do not use the Dog product (containing 2.5% moxidectin) on Cats.

WARNINGS:

Advantage Multi for Dogs: **For the first 30 minutes after application: Ensure that dogs cannot lick the product from application sites on themselves or other treated dogs, and separate treated dogs from one another and from other pets to reduce the risk of accidental ingestion. Ingestion of this product by dogs may cause serious adverse reactions including depression, salivation, dilated pupils, incoordination, panting, and generalized muscle tremors. In avermectin sensitive dogs[a], the signs may be more severe and may include coma and death[b].**

[a] Some dogs are more sensitive to avermectins due to a mutation in the MDR1 gene. Dogs with this mutation may develop signs of severe avermectin toxicity if they ingest this product. The most common breeds associated with this mutation include Collies and Collie crosses.

[b] Although there is no specific antagonist for avermectin toxicity, even severely affected dogs have completely recovered from avermectin toxicity with intensive veterinary supportive care.

Advantage Multi for Cats: **Do not use on sick, debilitated, or underweight cats. Do not use on cats less than 9 weeks of age or less than 2 lbs. body weight. Do not use on sick or debilitated ferrets.**

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. Dogs: Children should not come in contact with the application sites for two (2) hours after application. Cats: Children should not come in contact with the application site for 30 minutes after application.

Causes eye irritation. Harmful if swallowed. Do not get in eyes or on clothing. Avoid contact with skin. **Wash hands thoroughly with soap and warm water after handling.** If contact with eyes occurs, hold eyelids open and flush with copious amounts of water for 15 minutes. If eye irritation develops or persists, contact a physician. If swallowed, call poison control center or physician immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or physician. People with known hypersensitivity to benzyl alcohol, imidacloprid, or moxidectin should administer the product with caution. In case of allergic reaction, contact a physician. If contact with skin or clothing occurs, take off contaminated clothing. Wash skin immediately with plenty of soap and water. Call a poison control center or physician for treatment advice. The Safety Data Sheet (SDS) provides additional occupational safety information. For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call Bayer Veterinary Services at 1-800-422-9874. For consumer questions call 1-800-255-6826.

PRECAUTIONS: Do not dispense dose applicator tubes without complete safety and administration information. Use with caution in sick, debilitated or underweight animals. The safety of *Advantage Multi for Dogs* has not been established in breeding, pregnant, or lactating dogs. The safe use of *Advantage Multi for Dogs* has not been established in puppies and dogs less than 7 weeks of age or less than 3 lbs. body weight. *Advantage Multi for Dogs* has not been evaluated in heartworm-positive dogs with Class 4 heartworm disease.

Cats may experience hypersalivation, tremors, vomiting and decreased appetite if *Advantage Multi for Cats* is inadvertently administered orally or through grooming/licking of the application site. The safety of *Advantage Multi for Cats* has not been established in breeding, pregnant, or lactating cats. The effectiveness of *Advantage Multi for Cats* against heartworm infections *(D. immitis)* after bathing has not been evaluated in cats. Use of this product in geriatric cats with subclinical conditions has not been adequately studied. Ferrets: The safety of *Advantage Multi for Cats* has not been established in breeding, pregnant, and lactating ferrets. Treatment of ferrets weighing less than 2.0 lbs. (0.9kg) should be based on a risk-benefit assessment. The effectiveness of *Advantage Multi for Cats* in ferrets weighing over 4.4 lbs. (2.0 kg) has not been established.

ADVERSE REACTIONS: Heartworm Negative Dogs: The most common adverse reactions observed during field studies were pruritus, residue, medicinal odor, lethargy, inappetence and hyperactivity. **Heartworm Positive Dogs:** The most common adverse reactions observed during field studies were cough, lethargy, vomiting, diarrhea (including hemorrhagic), and inappetence. **Cats:** The most common adverse reactions observed during field studies were lethargy, behavioral changes, discomfort, hypersalivation, polydipsia and coughing and gagging. **Ferrets:** The most common adverse reactions observed during field studies were pruritus/scratching, scabbing, redness, wounds and inflammation at the treatment site; lethargy; and chemical odor.

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

Advantage Multi is protected by one or more of the following U.S. patents: 6,232,328 and 6,001,858.

NADA 141-251,141-254 Approved by FDA V-03/2016

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References

1. Brodbelt DC, Pfeiffer DU, Young LE, Wood JLN. Risk factors for anaesthetic-related death in cats: results from the confidential enquiry into peri-operative small animal fatalities (CEPSAF). *Br J Anaesth*. 2007;99(5):617-623.
2. Brodbelt DC, Pfeiffer DU, Young LE, Wood JLN. Results of the confidential enquiry into perioperative small animal fatalities regarding risk factors for anesthetic-related death in dogs. *J Am Vet Med Assoc*. 2008;233(7):1096-1104.
3. Matthews NS, Mohn TJ, Yang M, et al. Factors associated with anesthetic-related death in dogs and cats in primary care veterinary hospitals. *J Am Vet Med Assoc*. 2017;250(6):655-665.
4. Hofmeister EH, Herrington JL, Mazzaferro EM. Opioid dysphoria in three dogs. *J Vet Emerg Crit Care*. 2006;16(1):44-49.
5. Bednarski R, Grimm K, Harvey R, et al. AAHA anesthesia guidelines for dogs and cats. *J Am Anim Hosp Assoc*. 2011;47(6):377-385.
6. Kropf J, Hughes JL. Effect of midazolam on the quality and duration of anaesthetic recovery in healthy dogs undergoing elective ovariohysterectomy or castration. *Vet Anaesth Analg*. 2019;46(5):587-596.
7. Grubb T, Sager J, Gaynor J, et al. 2020 AAHA anesthesia and monitoring guidelines for dogs and cats. *J Am Anim Hosp Assoc*. 2020;56(2):59-82.
8. Becker WM, Mama KR, Rao S, Palmer RH, Egger EL. Prevalence of dysphoria after fentanyl in dogs undergoing stifle surgery. *Vet Surg*. 2013;42(3):302-307.
9. Mathews K, Kronen PW, Lascelles D, et al. Guidelines for recognition, assessment and treatment of pain: WSAVA Global Pain Council members and co-authors of this document. *J Small Anim Pract*. 2014;55(6):E10-E68.
10. Moore AD, Anghelescu DL. Emergence delirium in pediatric anesthesia. *Paediatr Drugs*. 2017;19(1):11-20.
11. Kanaya A, Kuratani N, Satoh D, Kurosawa S. Lower incidence of emergence agitation in children after propofol anesthesia compared with sevoflurane: a meta-analysis of randomized controlled trials. *J Anesth*. 2014;28(1):4-11.
12. Reid J, Nolan AM, Hughes JML, Lascelles D, Pawsom P, Scott EM. Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. *Anim Welfare*. 2007;16(S):97-104.
13. Calvo G, Holden E, Reid J, et al. Development of a behaviour-based measurement tool with defined intervention level for assessing acute pain in cats. *J Small Anim Pract*. 2014;55(12):622-629.
14. Hernandez-Avalos I, Mota-Rojas D, Mora-Medina P, et al. Review of different methods used for clinical recognition and assessment of pain in dogs and cats. *Int J Vet Sci Med*. 2019;7(1):43-54.
15. Lloyd JKF. Minimising stress for patients in the veterinary hospital: why it is important and what can be done about it. *Vet Sci*. 2017;4(2);22.
16. Gruen ME, Sherman BL. Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases (1995-2007). *J Am Vet Med Assoc*. 2008;233(12):1902-1907.
17. Gruen ME, Roe SC, Griffith E, Hamilton A, Sherman BL. Use of trazodone to facilitate postsurgical confinement in dogs. *J Am Vet Med Assoc*. 2014; 245(3): 296-301.
18. King C, Buffington L, Smith TJ, Grandin T. The effect of a pressure wrap (ThunderShirt) on heart rate and behavior in canines diagnosed with anxiety disorder. *J Vet Behav*. 2014;9(5):215-221
19. Cottam N, Dodman NH, Ha JC. The effectiveness of the anxiety wrap in the treatment of canine thunderstorm phobia: an open-label trial. *J Vet Behav*. 2013;8(3):154-161.
20. Ness TJ, Richter HE, Varner RE, Fillingim RB. A psychophysical study of discomfort produced by repeated filling of the urinary bladder. *Pain*. 1998;76(1-2):61-69.
21. Dyson DH, Doherty T, Anderson GI, McDonell WN. Reversal of oxymorphone sedation by naloxone, nalmefene, and butorphanol. *Vet Surg*. 1990;19(5): 398-403.
22. Court MH, Greenblatt DJ. Pharmacokinetics and preliminary observations of behavioral changes following administration of midazolam to dogs. *J Vet Pharmacol Ther*. 1992;15(4):343-350.
23. Stegmann GF, Bester L. Some clinical effects of midazolam premedication in propofol-induced and isoflurane-maintained anaesthesia in dogs during ovariohysterectomy. *J S Afr Vet Assoc*. 2001;72(4):214-216.
24. Gardos G. Disinhibition of behavior by antianxiety drugs. *Psychosomatics*. 1980;21(12):1025-1026
25. Posner LP, Burns P. Sedative agents: tranquilizers, alpha-2 agonists, and related agents. In: Riviere JE, Papich MG, eds. *Veterinary Pharmacology & Therapeutics*. 9th ed. Wiley-Blackwell; 2009:356-365.
26. Mathus-Vliegen EMH, de Jong L, Kos-Foekema HA. Significant and safe shortening of the recovery time after flumazenil-reversed midazolam sedation. *Dig Dis Sci*. 2014;59(8):1717-1725.
27. Costa RS, Karas AZ, Borns-Weil S. Chill protocol to manage aggressive & fearful dogs. *Clinician's Brief*. 2019;17(5):63-65.

References

Biller B, Berg J, Gerrett L, et al. 2016 AAHA oncology guidelines for dogs and cats. *J Am Anim Hosp Assoc.* 2016;52(6);181-204. doi:10.5326/JAAHA-MS-6570.

Clinkenbeard KD, Cowell RL, Tyler RD. Disseminated histoplasmosis in dogs: 12 cases (1981-1986). *J Am Vet Med Assoc.* 1988;193(11):1443-1447.

Cork LC, Morris JM, Olson JL, Krakowka S, Swift AJ, Winkelstein JA. Membranoproliferative glomerulonephritis in dogs with a genetically determined deficiency of the third component of complement. *Clin Immunol Immunopathol*. 1991;60(3):455-470.

DiBartola SP, Tarr MJ, Webb DM, Giger U. Familial renal amyloidosis in Chinese Shar-Pei dogs. *J Am Vet Med Assoc*. 1990;197(4):483-487.

Harley L, Langston C. Proteinuria in dogs and cats. *Can Vet J*. 2012;53(6):631-638.

Hood JC, Huxtable C, Naito I, Smith C, Sinclair R, Savige J. A novel model of autosomal dominant Alport syndrome in Dalmatian dogs. *Nephrol Dial Transplant*. 2002;17(12):2094-2098.

Hood JC, Savige J, Hendtlass A, Kleppel MM, Huxtable CR, Robinson WF. Bull terrier hereditary nephritis: a model for autosomal dominant Alport syndrome. *Kidney Int*. 1995;47(3):758-765.

IRIS Canine GN Study Group Diagnosis Subgroup, Littman MP, Daminet S, Grauer GF, Lees GE, van Dongen AM. Consensus recommendations for the diagnostic investigation of dogs with suspected glomerular disease. *J Vet Intern Med*. 2013;27(Suppl 1):S19-S26.

Lees GE, Helman RG, Kashtan CE, et al. A model of autosomal recessive Alport syndrome in English cocker spaniel dogs. *Kidney Int*. 1998;54(3):706-719.

Lees GE, Helman RG, Kashtan CE, et al. New form of X-linked dominant hereditary nephritis in dogs. *Am J Vet Res*. 1999;60(3):373-383.

Lees GE, Jensen WA, Simpson DF, et al. Persistent albuminuria precedes onset of overt proteinuria in male dogs with X-linked hereditary nephropathy. *J Vet Intern Med*. 2002;16(3):353.

Littman MP. Protein-losing nephropathy in small animals. *Vet Clin North Am Small Anim Pract.* 2011;41(1):31-62.

Mason NJ, Day MJ Renal amyloidosis in related English foxhounds. *J Small Anim Pract*. 1996;37(6):255-260.

Spano M, Zuliani D, Peano A, Bertazzolo W. Cladosporium cladosporioides-complex infection in a mixed-breed dog. *Vet Clin Pathol.* 2018;47(1):150-153.

Vaden SL, Elliot J. Management of proteinuria in dogs and cats with chronic kidney disease. *Vet Clin North Am Small Anim Pract*. 2016;46(6):1115-1130.

Vaden SL. Glomerular diseases. In: Ettinger SJ, Feldman EC, Côté E, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. Elsevier; 2017:1959-1972.

Wright NG, Nash AS, Thompson, H, Fisher EW. Membranous nephropathy in the cat and dog: a renal biopsy and follow-up study of sixteen cases. *Lab Invest*. 1981;45(3):269-277.

Feline Orthopedic Examination

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Orthopedic disease is common in cats.[1-4] The goal of an orthopedic examination is to identify the source of pain and/or lameness; however, this can be difficult in cats.

In dogs, limping is the most common complaint for musculoskeletal disease, and it is easy to ascertain that an orthopedic examination is needed. In cats, the most common presenting complaints for musculoskeletal disease are changes in attitude (eg, being fractious or less playful), poor grooming, urination or defecation outside of the litter box, or the pet owner's sense of undiagnosed illness in the cat; musculoskeletal disease may also affect mobility and flexibility, contributing to these signs.[2,5-7] Inability to induce cats to consistently walk as desired and difficulty differentiating pain from fear or anxiety-related behaviors can also be challenging. Despite these challenges, orthopedic examination is important for diagnosis and establishment of a treatment plan.

Some cats may require sedation or behavior-modifying drugs prior to presentation; anesthesia may be required for staff safety in extreme cases. Although commonly used medications (eg, gabapentin) might not impact examination except in subtle cases, significant sedation or anesthesia may be required if the patient has signs of pain (eg, arousal, increased heart and/or respiratory rate, elevated blood pressure, focal muscle tremors). Examination may also need to rely more heavily on observation of swelling and palpation of abnormalities.

Initially, it is important to observe posture, stance, and ambulation.[2] Most cats are not trained to walk on a leash, so the patient may need to be coaxed to walk. Observation of other behaviors may also help localize the problem. For example, cats with hip or back pain may be less willing to jump up on a chair or may attempt to jump and miss, or cats may stand on their pelvic limbs but keep their hips flexed and fully extend their hocks.

During examination, musculature should be palpated for symmetry.[2] Muscle atrophy, masses, and/or swelling can provide direction to a specific limb (especially if

observation of ambulation was not successful). Cats that tolerate examination can have unaffected limbs examined first, allowing observation of normal reactivity; this can help in detection of subtle reactions attributable to pain.[7] However, most cats only tolerate examination for a short period of time, so beginning with the unaffected limbs may not be prudent in all cases.

It is important to start at the distal aspect of the limbs and work proximally. Constant contact should be used, starting from the torso to the digits, as this can be less aversive than just reaching for the digits. Cats are less stressed and may be more cooperative when in a comfortable location or position (eg, reclining, standing, being held by the owner). Cats that fold the limbs under the body can have the chest or pelvis supported while the thoracic or pelvic limbs, respectively, are examined (***Figure 1***).

When examining a joint, spreading pressure over a wide area with multiple fingers or a palm can decrease the effect of pressure on bones and soft tissues, isolating the joint as the potential source of pain. Otherwise, very focal pressure may cause pain at the gripping point, which can confound assessment of joint pain. Normal range of motion and locations for palpating swelling are presented in the ***Table***, next page.

Assessment of the Shoulder, Hip, & Lumbar Region

Shoulders and hips cannot be palpated for effusion because of muscle coverage, and difficulty with isolation can make assessment challenging. For example, when the hips and shoulders are extended, the stifle and elbow are also extended, respectively, and the hips or shoulders are no longer isolated (***Figure 2***, page 77). This may make pain isolation especially difficult in the pelvic limbs when assessing for hip dysplasia, as the hips may not be the only source of pain.[8] As the hips are extended, the lumbosacral aspect of the back is also extended, and a pain response may be solely or partially attributed to osteoarthritis in the lumbar spine.

Back and hip pain can be differentiated using a combination of multiple aspects. For example, cats with lumbar pain typically do not have pain on flexion or abduction of the hip but do have pain on direct palpation of the back or extension of the pelvis with the hips in neutral or flexed position. Conversely, pain attributed to the hip may be present when the hip is abducted, but this movement will not impact other joints or the back. Similarly, in the forelimb, if the scapula is fixed in position, the humerus can be abducted to an ≈45-degree angle. This movement does not affect the distal joints, unlike extension of the shoulder. The abduction angle should be symmetrical with the opposite side, and excessive abduction may indicate collateral ligament damage.

Continued ▶

▲ **FIGURE 1** Cat with elbow flexion. The chest is supported, the elbow is flexed, and the shoulder is maintained in a neutral position.

TABLE

NORMAL LANDMARKS FOR EFFUSION & RANGE OF MOTION

Joint	Flexion Landmarks	Extension Landmarks	Joint Effusion
Phalanges	Digital and metacarpal or metatarsal pads touch	Normal standing position; claws should be extendable	Externally palpable dorsally
Carpus	Paw pads touch the antebrachium	Normal standing position just past 180 degrees	Palpated over the dorsal carpal surface of the small carpal bones when palpated in slight flexion
Elbow	Carpus touches the shoulder	Straight limb from shoulder to carpus	Palpated by finding the lateral epicondyle and palpating caudally toward the ulna
Shoulder	Elbow travels lateral to the fourth rib toward the ventral aspect of the scapula	Limb points out past the head, almost parallel to the line of the spine	Not palpable
Hock	When stifle is allowed to flex, the dorsal metatarsals touch the tibia. The hock will only flex slightly if the stifle is not allowed to flex when the hock is flexed (tibial compression test).	Straight limb from tibia to metatarsals	The transition of bone palpated from the medial and lateral malleolus caudally to the calcaneus
Stifle	Tuber calcaneus touches the ischiatic tuber	Limb is straight from femur to tibia when visualizing from the lateral direction	Palpated by feeling both sides of the patellar ligament
Hip	Stifle touches the ventral ilium	Femur extends caudally, almost parallel with the spine	Not palpable
Cervical spine	Head touches the chest and both left and right shoulders	Head manipulated, with the nose pointed dorsally	Not palpable
Thoracolumbar spine	Knees touch elbows to determine spinal flexion from lateral direction	Straight spine or slight ventral curve	Not palpable

Instability

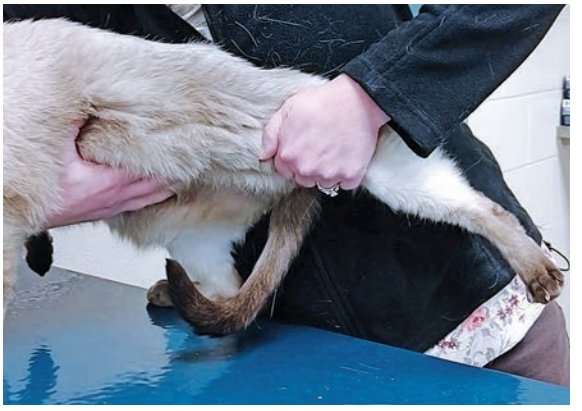
Separate evaluation for instability should be performed in cats with swelling, history indications (eg, specific trauma), or unremarkable physical examination. Medial and lateral stress should be used to test instability of the collateral ligaments, except in the hip where collateral ligaments are not present. Palpating the unaffected side can be helpful in distinguishing normal from abnormal movement. The joint angle should be held constant while palpating for collateral ligament instability. Allowing flexion or extension while palpating for varus and valgus instability can make detection of abnormalities difficult; this is easiest in a neutral joint angle. However, the hock may be tested separately in both flexion and extension to determine which ligament is more specifically affected and to ascertain subtle abnormalities. The talofibular ligament is the primary stabilizer in flexion, but the long and short collateral ligaments stabilize extension. Dorsal or palmar/plantar ligament abnormalities can also be detected by stabilizing the tibia or radius and placing pressure on the metacarpals or metatarsals both cranially and caudally.

Cruciate & Patellar Disease

Although cats are not predisposed to cranial cruciate ligament rupture or patellar luxation, occasional prevalence necessitates careful evaluation. A cranial cruciate ligament rupture can be detected using the tibial compression test or the cranial drawer test. Presence of patellar luxation can be detected by applying gentle pressure medially and laterally to determine whether the patella luxates during range of motion; this is easiest in stifle extension and can be performed in flexion in some instances. Cats generally have more patellar movement medially and laterally than dogs; however, the patella rebounds to the correct position when not being held.

Tibial compression test is positive if the tibial tuberosity moves forward in relation to the femoral condyles when the hock is flexed. The cranial drawer test can be used to determine cranial cruciate ligament rupture (ie, cranial drawer) or caudal cruciate ligament rupture (ie, caudal drawer). To determine whether reactions were coincidental (ie, attributable to restraint) or attributable to pain, these procedures may need to be repeated, depending on the severity of pain and clinical confidence in the results.

Continued ▶



▲ **FIGURE 2** Cat with hip extension. Simultaneous extension of the hock and stifle can be seen.

Cats generally have more patellar movement medially and laterally than dogs; however, the patella rebounds to the correct position when not being held.

STEP-BY-STEP FELINE ORTHOPEDIC EXAMINATION

STEP 1

Coax the cat to walk around the examination room. Observe the cat's locomotion and posture to evaluate for the presence of limping, abnormal gait, weight shifting, mechanical abnormalities (eg, dropped hocks), and/or neurologic disease (eg, lameness, weakness, ataxia). Observe for other clinical behaviors that may assist in lesion localization.

Author Insight

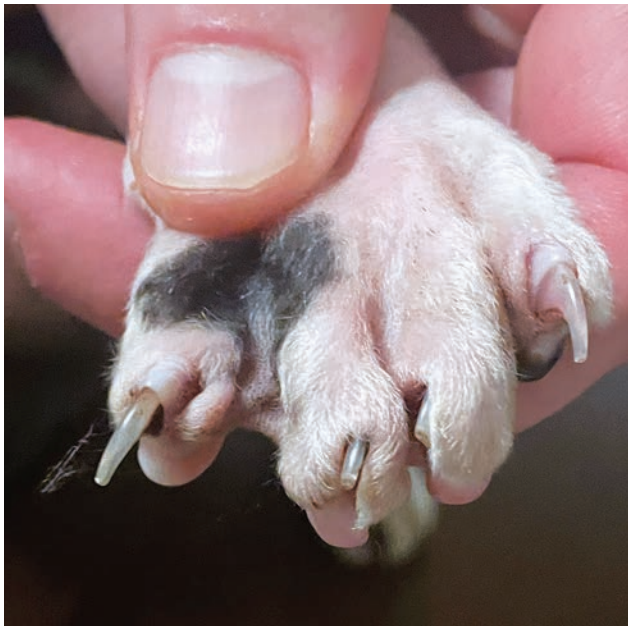
The cat can be filmed at home or in the examination room to help in evaluation of locomotion. Viewing the film in slow motion can help in detection of important nuances in movement that might be overlooked when viewed at normal speed.

STEP 2

Palpate the musculature for symmetry, and look for muscle atrophy, masses, and/or swelling that can provide direction to a specific limb. If the cat is tolerating the examination well, examine the unaffected limbs first and observe subsequent behaviors.

STEP 3

Start at the distal aspect of the limbs and work proximally. Begin with the digits, and inspect the nails (use gentle dorsal pressure on the digit to extend the nail) and the interdigital skin for injury, swelling, draining tracts, or redness. Flex and extend only the digits while isolating the joints distal to the metacarpophalangeal or metatarsophalangeal joints. If the cat resists, vocalizes, demonstrates aggression, or attempts escape with flexion of all the digits, then isolate, flex, and extend each individual digit in turn.



STEP 4

As the examination proceeds proximally, palpate the bones, soft tissues, and joints for pain, swelling, or instability. Press on the distal bone and soft tissue using broad pressure to flex and extend the joints while ensuring the other joints are at a neutral angle.

Author Insight

Palpating the soft tissue and bone prior to assessing joint range of motion can help differentiate the source of the pain (eg, bone vs joint).

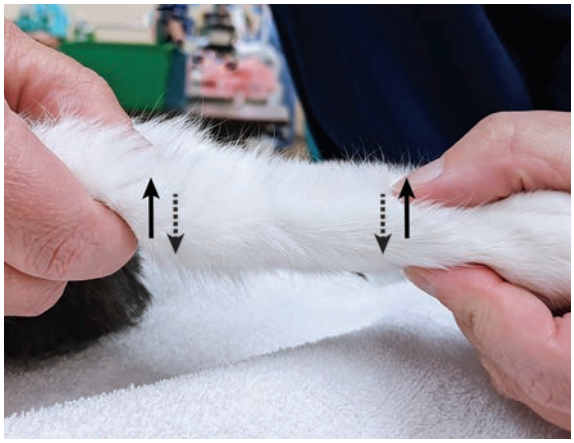
STEP 5

To isolate the lumbar spine for pain evaluation, with the cat in lateral recumbency, palpate the small divot palpable on the dorsal midline caudal to the L7 dorsal spinous process between the ilial wings or the lumbosacral area (***A***), and press the feet proximally to flex the hips and extend the lumbar spine (***B***).

Continued ▶

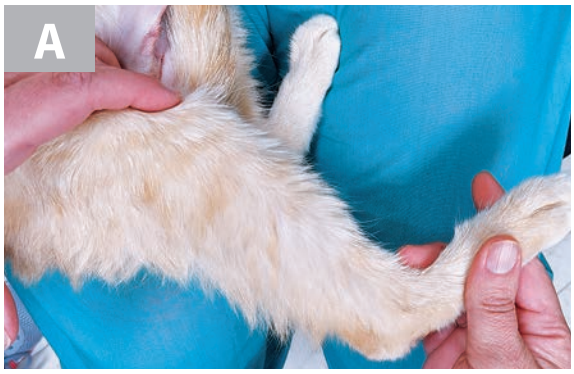
STEP 6

If a special examination for instability is indicated, use medial and lateral stress to test instability of the joint's collateral ligaments for all joints distal to the shoulder or hip. When examining the hindlimb, place the hands proximal and distal to the hock. Stress the medial collateral ligament by introducing pressure up (***solid arrows***), and stress the lateral collateral ligament by introducing pressure down (***dashed arrows***). Do not allow the patient to move while in flexion or extension and while the collateral ligaments are being stressed.



STEP 7

For suspected cranial cruciate ligament rupture, conduct a tibial compression test or a cranial drawer test. During the tibial compression test, prevent the stifle from flexing as the hock is flexed (***A***). Rest the index finger on the tibial tuberosity to palpate for cranial movement. Perform the cranial drawer test by placing the thumb of the proximal hand on the lateral fabella and the index finger on the patella (***B***), then place the thumb of the distal hand on the fibular head and the index finger on the tibial tuberosity, and hold the femur in place while moving the tibia cranially or caudally.



References

1. Hardie E, Roe S, Martin F. Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994–1997). *J Am Vet Med Assoc*. 2002;220(5):628-632.
2. Kerwin S. Orthopedic examination in the cat. *J Feline Med Surg*. 2012;14(1):6-12.
3. Lascelles BDX, Henry JB, Brown J, et al. Cross-sectional study of the prevalence of radiographic degenerative joint disease in domesticated cats. *Vet Surg*. 2010;39(5):535-544.
4. Clarke SP, Mellor D, Clements DN, et al. Radiographic prevalence of degenerative joint disease in a hospital population of cats. *Vet Rec*. 2005;157(25):793-799.
5. Clarke SP, Bennett D. Feline osteoarthritis: a prospective study. *J Small Anim Pract*. 2006;47(8):439-445.
6. Bennett D, Morton CA. A study of owner observed behavioural and lifestyle changes in cats with musculoskeletal disease before and after analgesic therapy. *J Feline Med Surg*. 2009;11(12):997-1004.
7. Lascelles BDX, Bernie HD, Roe S, et al. Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *J Vet Intern Med*. 2007;21(3):410-416.
8. Keller GG, Reed AL, Lattimer JC, Corley EA. Hip dysplasia: a feline population study. *Vet Radiol Ultrasound*. 1999;40(5):460-464.

LEPTOSPIROSIS: THE ESSENTIAL NEED FOR TESTING

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NATALIE L. MARKS, DVM, CVJ

This past year has unveiled many challenges around the world, but if it has highlighted anything in medicine, it is that zoonotic disease (ie, disease spread from animals to humans) is a major threat to the health of the human population. Veterinarians and public health officers are responsible for protecting their patients and clients and should focus on reducing this threat by using parasite preventives and vaccination strategies to protect dogs from diseases that may pose a threat to humans.

Leptospirosis is the most widespread zoonotic disease worldwide,[1] and although vaccination with a quadrivalent vaccine is core to patient and family protection, a strong prevention strategy must also include detection of positive patients through testing. In one study, 10% of humans infected with leptospirosis were infected from contact with their pets.[2] Although these canine infections may be due to a lack of appropriate vaccination, they also represent a subset of patients that are frequently being missed in the profession.

Many patients can be presented with noticeable clinical signs of acute illness such as fever, inappetence, and vomiting, but leptospirosis can also create a worrisome chronic carrier status in dogs characterized by subclinical urinary shedding.[3] This urination creates a reservoir of leptospires in the home environment, placing young children and family members at increased risk for transmission. Without proper testing and treatment, these leptospires may be shed for months in the urine of patients, creating a consistent risk for zoonosis in the environment.[1]

Thankfully, several testing options are now available, including reference laboratory PCR and microscopic agglutination testing, as well as the more recent point-of-care testing for in-clinic use. Because there are limitations to all tests in that none are 100% sensitive (ie, a negative test in an acutely ill patient does not always rule out disease),[4] it is always important to consider the timeline for a patient's onset of clinical signs and the accuracy of each test before it is performed and during interpretation.

REFERENCES

1. Sykes JE, Hartmann K, Lunn KF, Moore GE, Stoddard RA, Goldstein RE. 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2011;25(1):1-13.
2. Meites E, Jay MT, Deresinski S, et al. Reemerging leptospirosis, California. *Emerg Infect Dis*. 2004;10(3):406-412.
3. Miotto BA, Guilloux AGA, Tozzi BF, et al. Prospective study of canine leptospirosis in shelter and stray dog populations: identification of chronic carriers and different *Leptospira* species infecting dogs. *PLoS One*. 2018;13(7): e0200384.
4. Troìa R, Balboni A, Zamagni S, et al. Prospective evaluation of rapid point-of-care tests for the diagnosis of acute leptospirosis in dogs. *Vet J*. 2018;237:37-42.

Without proper testing and treatment, these leptospires may be shed for months in the urine of patients, creating a consistent risk for zoonosis in the environment.[1]

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Sudden Onset of Fear & Panic in a Bernese Mountain Dog

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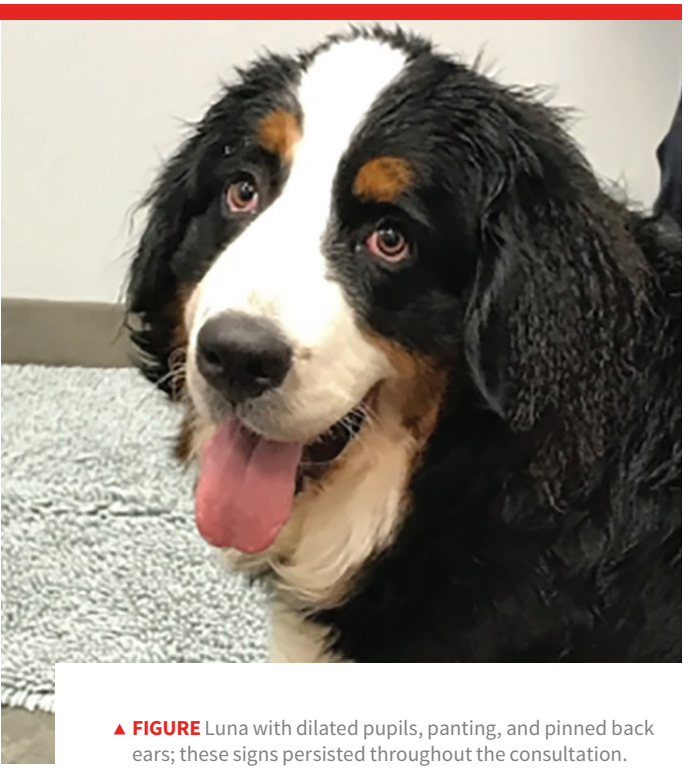

▲ **FIGURE** Luna with dilated pupils, panting, and pinned back ears; these signs persisted throughout the consultation.

Luna, a 9-month-old, 60-lb (27-kg) intact female Bernese mountain dog, had a sudden onset of severe fear and panic toward new elements in her environment, unfamiliar humans, and riding in a car after she fell from a moving vehicle at 4 months of age.

Prior to Luna falling out of the car, her owners reported that she was normal, quickly accepted unfamiliar humans, and appeared to enjoy riding in the car. After falling, Luna began to startle, back up, bark, and growl when encountering novel items (eg, a plastic bag blowing in the wind); pant, bark, growl, and attempt to hide when unfamiliar humans entered the home; and back up, cower, tremble, pant, and profusely drool when being lifted into and riding in the car. She also appeared fearful when walking underneath objects (eg, trees, entryways). These behaviors continued for the next 5 months, at which time she was presented to a behavior clinic.

Physical Examination & Diagnostics

Luna was initially presented to an emergency veterinary clinic after the fall. Diagnostic evaluation (including CBC, serum chemistry profile, and urinalysis) was performed, and all results were within normal limits. Because there was possible head trauma from the fall, she was also referred to a neurologist where a brain MRI was completed—results were also within normal limits.

Physical and neurologic examination findings at the time of presentation to the behavior clinic were also within normal limits. Behavior signs in the examination room included panting, pinning her ears back, cowering near her owners, and being unwilling to interact with staff or take treats during the consultation; her pupils were also dilated (***Figure***). An FAS (ie, Fear, Anxiety, and Stress) spectrum and pain algorithm was used (see ***Suggested Reading***, page 71), on which Luna scored an FAS 4: severe.

DIAGNOSIS:

CHRONIC POST-TRAUMATIC STRESS DISORDER

Based on patient history, and because the behavior issues were persistent and did not resolve, chronic post-traumatic stress disorder (PTSD) was diagnosed.

Secondary diagnoses included generalized anxiety disorder (based on the patient spending most of her time in an anxious state), global phobia (ie, persistent and excessive fears that are potentially irrational in nature), neophobia (ie, exaggerated fear response to novel items), and fear-based aggression (ie, distance increasing body postures and vocalizations [eg, barking, growling, snarling, lunging, nipping, snapping, biting] toward unfamiliar humans and dogs).

Treatment

Treatment for behavior issues should include environmental management, behavior modification, and medical therapy.

DESENSITIZATION & COUNTERCONDITIONING FOR A TRIGGER

To address Luna's fear of plastic bags, the distance at which she had no negative reaction toward the bag was determined. The bag was presented to her at that distance, her owner fed her a high-value reward, and the bag was removed when she stopped feeding. Once Luna developed a positive emotional response to the presence of the bag (as a result of receiving a high-value reward), criteria were increased, including bringing the bag closer to her or having the bag make noise or move. Luna was kept under threshold for reaction, and focus was kept on creating a positive emotional response before moving to next steps.

DSCC = desensitization and counterconditioning
NT = neurotransmitter
PTSD = post-traumatic stress disorder

Environmental Management

Environmental management is important for elimination of unwanted behavior, as well as elimination (as much as feasible) of fear, anxiety, and frustration that are often the underlying cause of behavior concerns. Learning can only take place when the patient is not experiencing a high level of emotional arousal; thus, environmental management is the first step in treatment, before behavior modification can be started.

Luna's owners were instructed to attempt to avoid triggering situations during the treatment period, including not having guests in the home, not driving Luna in the car, and taking Luna on walks during nonpeak hours. Her owners were told to remove her from triggering encounters as quickly as possible.

Behavior Modification

Behavior modification involves either teaching an alternate incompatible behavior to replace the unwanted behavior or altering the emotional state from one that is negative to one that is positive or neutral (ie, desensitization and counterconditioning [DSCC]).

Initial behavior modification techniques were focused on additional management strategies, including teaching Luna to wear a basket muzzle and perform an emergency U-turn (ie, a 180-degree turn away from the trigger/stimulus). Further behavior modification was delayed until Luna's anxiety was low enough to remain under threshold (ie, the level at which emotional arousal is too high and a negative reaction occurs). Once Luna's anxiety was under control, DSCC for her triggers could begin (see ***Desensitization & Counterconditioning for a Trigger***).

Medical Therapy

Environmental management alone is impractical, and complete compliance is difficult in patients with numerous triggers, as with Luna and most patients with this set of diagnoses. Anxiolytic medication is thus necessary. Medical therapy is often multimodal, targeting ≥1 neurotransmitters

(NTs) involved in fear and anxiety and includes serotonin (ie, coping NT), dopamine (ie, pleasure/activation NT), γ-aminobutyric acid (ie, inhibitory NT), and norepinephrine (ie, NT involved in fight/flight modulation).

Treatment for dogs with chronic PTSD and other phobias can be challenging, and the correct medications and products are needed for behavior modification.

Luna was started on the following:

- Sertraline (25 mg twice daily [≈1 mg/kg PO every 12 hours]), which was chosen because it is a selective serotonin reuptake inhibitor that targets serotonin and dopamine increases via inhibition of reuptake in the postsynaptic cleft.[1] In humans, sertraline is approved for use in patients with PTSD and social phobias.[2-4]
- Alprazolam (1-3 mg PO prior to or immediately after any panic-inducing situation [≈0.04-0.1 mg/kg PO every 6-8 hours as needed]), which is shown to be effective in treating dogs with noise phobia and often useful for treatment of other phobia disorders (eg, noise phobia)[5,6]
- α-casozepine (450 mg; used as directed based on patient weight), which is used for calming effects in dogs with anxiety disorders[7]
- Pheromone collar (used as directed by the manufacturer); maternal-appeasing pheromones have been shown to help dogs with noise phobias and other anxiety disorders (eg, travel anxiety).[8-10]

Nutraceuticals and pheromones may augment medical therapy and potentially improve outcomes when combined with other treatment modalities.[11]

After 4 weeks, sertraline was increased to 50 mg twice daily (≈2 mg/kg PO every 12 hours) based on an ≈60% reduction in intensity of fear and anxiety, as well as a continued need for improvement. All other drugs and products were continued at the starting dosages. Luna's owners reported a decrease in the intensity of reactions to triggers and slightly decreased time of recovery, but attempts at DSCC were still unsuccessful. Management was still difficult due to the numerous triggers Luna experienced daily; this was partly due to living in an apartment complex in a major metropolitan area and the need to walk Luna for elimination purposes on a busy street.

Prognosis & Outcome

Once Luna's anxiety was lowered and she was able to be under threshold while at a reasonable distance from triggering situations, a program of DSCC to specific triggers (eg, riding in a car, meeting new people, going through thresholds and under trees) was implemented.

Despite moderate improvement in fear intensity and ability to recover when triggered, Luna's owners chose to relinquish her because they lived in an urban area in which she was exposed to triggers daily and because they were first-time dog owners who felt overwhelmed by her continued need for behavioral care. Luna's breeder assisted in rehoming her with a family in a suburban area in which management could be more easily accomplished. Luna had significant progress with the new family, presumably due to the combined effect of being in a new environment, ongoing medical therapy, and the new owner's commitment to the prescribed behavior modification plan. Alprazolam was rarely

TREATMENT AT A GLANCE

- Any possible medical etiology should be ruled out, especially in patients with a sudden change in behavior.
- Strict environmental management should be implemented to avoid unwanted behavior and keep the patient under threshold during treatment.
- Appropriate psychotropic medications and products should be considered to help reduce fear, anxiety, and stress.
- Behavior modification, including DSCC, with the assistance of a board-certified veterinary behaviorist or other qualified positive-reinforcement–based trainer can be helpful.

needed; however, her owners continued sertraline and other products because of Luna's progress and the owner's hesitance for potential setbacks.

Discussion

Canine PTSD is diagnosed based on the patient experiencing a potentially traumatizing event and subsequently developing signs like hypervigilance, aggression, compulsive disorders, sleep disturbance, increased startle response, fear, avoidance, and/or withdrawal. These signs persist >1 month after the traumatic event and are not present prior to the event. Similar experiences in humans should be used as criteria when diagnosing PTSD. Prevalence of PTSD in dogs is widely unknown due to lack of retrospective studies.[12]

Sudden onset of behavior is usually an indicator that a thorough medical workup is needed. Once medical etiologies have been ruled out and diagnostic criteria for behavior disorders are met, treatment can be started to alleviate and modify signs.

TAKE-HOME MESSAGES

- Medical etiologies should always be considered and ruled out when there is a sudden change in behavior.
- Traumatic events can cause PTSD in companion animals similar to that seen in humans.[12]
- Treatment for PTSD and other behavior problems should include a 3-part approach (ie, environmental management, behavior modification, medical therapy).
- Behavior modification, which is key for behavior disorders, cannot proceed until triggers do not immediately push the patient over their threshold.
- Psychotropic medications and products can positively impact patient well-being.
- Some owners may be unable or unwilling to care for a patient with behavior disorders.
- Improved living environment can impact treatment outcomes.

See page 71 for references and suggested reading.

PTSD = post-traumatic stress disorder

Mirataz®
(mirtazapine transdermal ointment)

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION: Federal law (USA) 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: Mirataz is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION: Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days. Wear disposable gloves when applying Mirataz. Alternate the daily application of Mirataz between the left and right inner pinna of the ears. **See Product Insert for complete dosing and administration information.**

CONTRAINDICATIONS: Mirataz is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients. Mirataz should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS: Not for human use. Keep out of reach of children. **Wear disposable gloves when handling or applying Mirataz to prevent accidental topical exposure.** After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing. In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention. In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS: Do not administer orally or to the eye. Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See **Animal Safety** in the product insert). Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure. Upon discontinuation of Mirataz, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat. Mirataz has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Mirataz has not been evaluated in cats that are intended for breeding, pregnant, or lactating cats.

ADVERSE REACTIONS: In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. **See Product Insert for complete Adverse Reaction information.** To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Dechra at 888-933-2472. 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/reportanimalae**.

EFFECTIVENESS: The effectiveness of Mirataz (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds. Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz to vehicle control. A total of 230 cats were enrolled and received either Mirataz (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear. A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Mirataz group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit. At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

STORAGE: Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED: Mirataz is supplied in a 5 gram aluminum tube.

MANUFACTURED FOR:
Dechra Veterinary Products
7015 College Boulevard, Suite 525
Overland Park, KS 66211 USA

US Patent 10,603,272

Approved by FDA under NADA # 141-481
NDC 86078-686-01

Rev. August 2020
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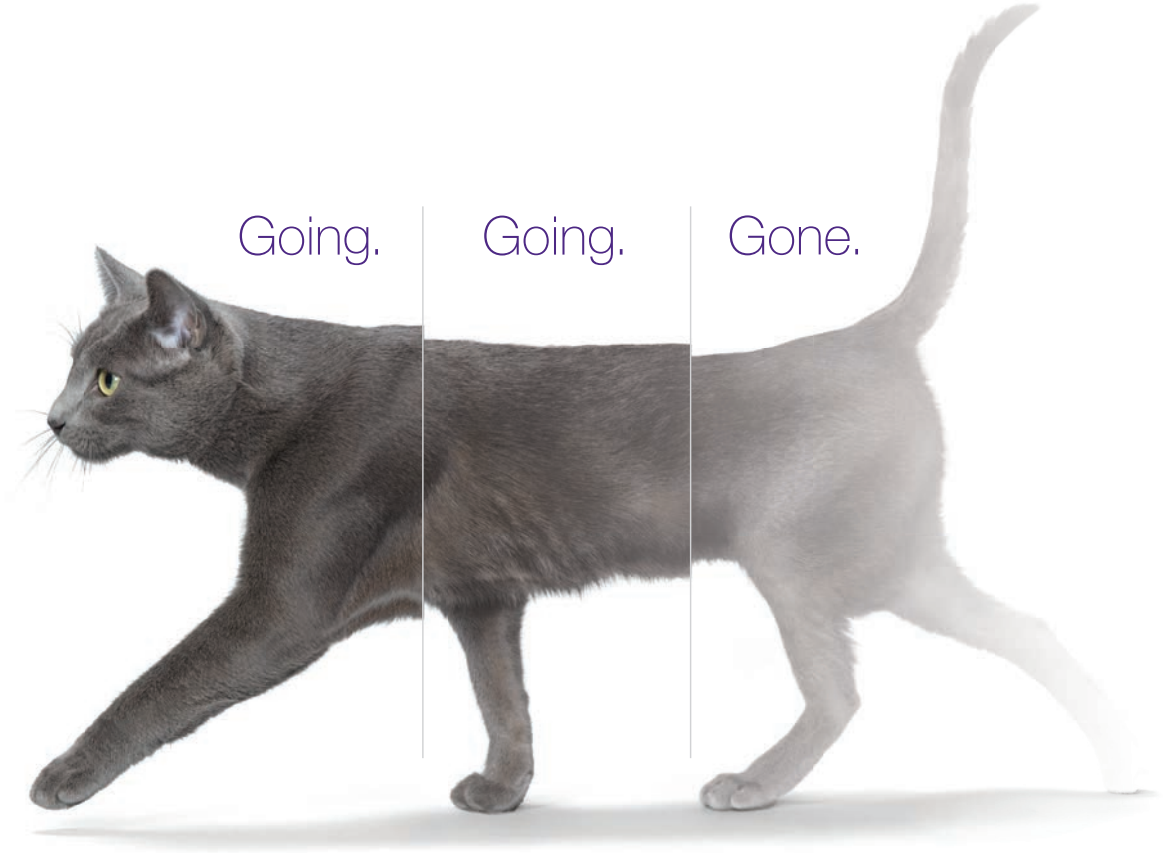
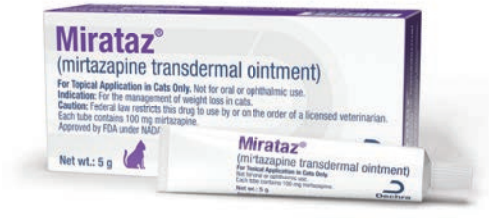


With unintended weight loss, you can't afford to wait.

Take control with Mirataz® (mirtazapine transdermal ointment).

Prolonged inadequate nutrition may be more detrimental to patients than the primary disease process triggering the weight loss.[1] Mirataz lets you take control. As the first and only FDA-approved transdermal medication for the management of feline weight loss, Mirataz increases body weight by 3.9% in as little as 14 days in an easy-to-apply transdermal ointment.[2] Learn more at www.Mirataz.com.

Mirataz®
(mirtazapine transdermal ointment)



For Veterinary Technical Support, contact Dechra Veterinary Products at:
866-933-2472 | www.dechra-us.com | support@dechra.com

Important Safety Information

Mirataz® (mirtazapine transdermal ointment) is for topical use in cats only under veterinary supervision. Do not use in cats with a known hypersensitivity to mirtazapine or any of the excipients. Do not use in cats treated with monoamine oxidase inhibitors (MAOIs). Not for human use. Keep out of reach of children. Wear gloves when handling/applying, wash hands after and avoid contact between the treated cat and people or other animals for 2 hours following application. Use with caution in cats with hepatic and kidney disease. Cat's food intake should be monitored upon discontinuation. Safety has not been evaluated in cats less than 2 kg, less than six months of age or in breeding, pregnant or lactating cats. The most common adverse reactions observed during clinical trials were application site reactions, behavioral abnormalities (vocalization and hyperactivity) and vomiting. **For additional safety information, see brief summary of prescribing information on page 86.**

References: 1. Agnew W, Korman R. Pharmacological appetite stimulation: rational choices in the inappetent cat. *J Feline Med Surg.* 2014;16(9):749-756. **2.** Poole M, Quimby JM, Hu T, et al. A double-blind, placebo-controlled, randomized study to evaluate the weight gain drug, mirtazapine transdermal ointment, in cats with unintended weight loss. *J Vet Pharmacol Ther.* 2019;42(2):179-188. doi:10.1111/jvp.12738.

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PEER REVIEWED **ADVERTORIAL**

Management of Chronic Kidney Disease in Cats

Dr. Vivian Yau,
DVM, DACVIM (SAIM)
Medical Director
Veterinary Specialty Group
of Glendora

Chronic kidney disease (CKD) diagnosis requires serum biochemical analysis (persistent azotemia, increased serum symmetric dimethylarginine [SDMA] concentration), urinalysis (low urine specific gravity, proteinuria) and imaging (kidney structural changes). Once CKD is confirmed, the next step is staging according to the guidelines from the International Renal Interest Society (IRIS; iris-kidney.com). The IRIS stages 1 to 4 are based on serum creatinine and SDMA concentrations. There is also sub-staging based on the degree of proteinuria and hypertension. Recent improvement in diagnostic testing has led to early detection and treatment in our patients with CKD.

The following are key considerations in the treatment of CKD in cats:

Nutrition

Early nutritional intervention is the most important aspect in the treatment of CKD. Therapeutic kidney diets are the cornerstone of CKD management (see Table 1). Kidney diets are modified to varying levels in phosphorus, protein, potassium and sodium, and may have increased levels of omega-3 fatty acids, antioxidants and water-soluble vitamins. Some kidney diets also provide L-carnitine or enhanced protein levels to help maintain body condition and muscle health.

In a study by Elliott et al., client-owned cats with stable CKD were fed an adult maintenance diet (n = 21) or a lower-protein/phosphorus kidney diet (n = 29). Use of the kidney diet helped reduce plasma phosphate, blood urea nitrogen, and parathyroid hormone concentrations. The median survival time for cats receiving a kidney diet was 633 days (1.7 years) compared with 264 days (0.7 years) for cats receiving an adult maintenance diet.[1]

Early nutritional intervention is the most important aspect in the treatment of CKD.

In a study by Ross et al., cats with IRIS stage 2 and 3 CKD were fed a therapeutic kidney diet (n = 22) or an adult maintenance diet (n = 23). In the therapeutic diet group, no cats experienced a uremic crisis and no renal-related deaths occurred, whereas 26% of cats had a uremic crisis and 21.7% of cats died of renal-related causes in the adult maintenance diet group.[2]

To improve acceptance of kidney diets, slow transition is necessary. Do not introduce a kidney diet alone to a sick cat to minimize risk for food aversion. It is important to minimize nausea and try to increase diet acceptance by considering forms, textures, flavors and temperature. Sometimes, the use of appetite stimulants may be necessary. Transdermal mirtazapine has been FDA-approved to manage unintended weight loss, and significantly increased appetite, reduced vomiting, and promoted weight gain in cats with CKD.[3]

Proteinuria

Survival time in azotemic cats was shorter with severe proteinuria and development of azotemia was significantly associated with proteinuria in non-azotemic cats .[4,5] It is important to manage proteinuria (urine protein to creatinine ratio >0.04) with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[6]

Hypertension

Hypertension can cause more rapid decline in renal function. Telmisartan as a single agent is FDA-approved to control hypertension in cats with CKD. Amlodipine was used traditionally to control hypertension in cats, but it can activate the renin-angiotensin-aldosterone system and may cause rebound hypertension. Continued research is ongoing.[7]

CKD - Mineral and bone disorder

The use of a restricted-phosphorus kidney diet alone may control serum phosphate concentrations. However, persistent hyperphosphatemia requires intestinal phosphate binders, such as aluminum hydroxide and others.[8]

Persistent hyperphosphatemia can lead to soft tissue mineralization and progression of CKD. In a study by Ross et al., cats with induced kidney disease were divided into 2 groups and fed either a normal- or low-phosphorus diet. Those that received a normal phosphorus diet had evidence of renal mineralization, fibrosis, and mononuclear cell infiltrates. Those that received a low phosphorus diet had mild to no histologic changes.[9]

Hyperphosphatemia can also reduce calcitriol and increase fibroblast growth factor-23 (FGF-23) secretion, promoting hyperparathyroidism and bone pathology.[8]

For therapeutic targets, recommended phosphorus levels are between 2.7 and 4.6 mg/dl with IRIS stage 2 CKD, less than 5 mg/dl with IRIS stage 3 CKD and less than 6 mg/dl with IRIS stage 4 CKD.[6]

Gastrointestinal disturbance

Cats with CKD have been shown to develop gastric mineralization and gastric gland hypertrophy.[10] A therapeutic kidney diet may help lessen gastrointestinal signs in some cats by managing hydration, hypokalemia, and acidosis, but anti-nausea medications are often necessary in late-stage CKD.

Hypokalemia

Hypokalemia is common in cats with IRIS stage 3 and 4 CKD. Maintaining potassium concentration in the middle or upper half of the laboratory reference range is recommended. Oral supplementation with potassium gluconate or potassium citrate is recommended if persistent hypokalemia is noted despite the use of a potassium-supplemented kidney diet.[11,12]

Anemia

Moderate to severe non-regenerative anemia can develop in cats with late-stage CKD. Cats will have weakness, lethargy, cold intolerance, and anorexia. The use of iron supplementation with or without an erythropoiesis-stimulating agent is recommended, with packed cell volume greater than 25% as the therapeutic target.[8]

Metabolic acidosis

A therapeutic kidney diet may help address acidosis secondary to CKD. In late-stage CKD, alkalinizing agents such as sodium bicarbonate or potassium citrate may be necessary to address metabolic acidosis, which also contributes to inappetence.[8]

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TABLE 1: CURRENT THERAPEUTIC KIDNEY DIETS FOR CATS (TYPICAL ANALYSIS FOR 100 KCAL)

DIET (DRY)	CALORIES (kcal/cup)	PHOSPHORUS (mg)	PROTEIN (g)	CARBOHYDRATE (g)
BLUE NVD K+M	425	130	6.88	9.67
Hill's k/d Early Support	536	127	7.7	8.7
Hill's k/d with Chicken	541	116	6.8	9.1
Hill's k/d with Ocean Fish	444	116	6.7	9.1
Hill's k/d + Mobility	484	116	6.6	9.7
Purina NF Early Care	494	90	8.95	8.37
Purina NF Advanced Care	536	90	6.92	9.51
Royal Canin Renal Support A	345	110	5.86	11.2
Royal Canin Renal Support F	373	110	6.55	10.5
Royal Canin Renal Support S	398	100	5.84	9.37
Royal Canin Renal Support + HP	402	110	6.07	9.76

DIET (CAN)	CALORIES (kcal/can)	PHOSPHORUS (mg)	PROTEIN (g)	CARBOHYDRATE (g)
BLUE NVD K+M	153	110	6.13	11.65
Hill's k/d Early Support	79	133	7.6	7.7
Hill's k/d Chicken & Vegetable Stew	70	111	6.8	8.7
Hill's k/d Vegetable & Tuna Stew	77	115	7.1	8.8
Hill's k/d Pate with Chicken	177	124	7.6	9.8
Hill's k/d + Mobility	68	108	6.6	8.5
Purina NF Early Care	162	110	9.49	7.67
Purina NF Advanced Care	165	90	6.69	8.96
Royal Canin Renal Support D	97	80	6.29	4.09
Royal Canin Renal Support E	171	90	6.64	5.4
Royal Canin Renal Support T	82	100	6.25	5.97

Source for diet information: BLUE Natural Veterinary Diet Product Guide 6-2020, Royal Canin Veterinary Health Nutrition Product Book 2019, Hill's Key to Clinical Nutrition 2018, Purina ProPlan Veterinary Diets Product Guide 2020

References:

[1] Elliott J, Rawlings JM, Markwell PJ, et al. Survival of cats with naturally occurring chronic renal failure: Effect of dietary management. *J Small Anim Pract* 2000; 41(6):235-242.

[2] Ross SJ, Osborne CA, Kirk CA, et al. Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. *JAVMA* 2006; 229(6):949-957.

[3] Quimby J, Lunn KF. Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: a masked placebo-controlled crossover clinical trial. *Vet J* 2013; 197(3): 651-655.

[4] Syme HM, Markwell PJ, Pfeiffer D, et al. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. *J Vet Intern Med* 2006; 20(3):528-535.

[5] Jepson RE, Brodbelt D, Vallance C, et al. Evaluation of predictors of the development of azotemia in cats. *J Vet Intern Med* 2009; 23(4):806-813.

[6] IRIS Treatment Recommendations for CKD in Cats (2019); iris-kidney.com.

[7] Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. *J Vet Intern Med* 2019; 33(2):363-382.

[8] Sparkes AH, Caney S, Chalhoub S, et al. ISFM consensus guidelines on the diagnosis and management of feline chronic kidney disease. *J Fel Med Surg* 2016; 18:219-239.

[9] Ross LA, Finco DR, Crowell WA. Effect of dietary phosphorus restriction on the kidneys of cats with reduced renal mass. *Am J Vet Res* 1982; 43(6):1023-1026.

[10] McLeland SM, Lunn KF, Duncan CG, Refsal KR, Quimby JM. Relationship among serum creatinine, serum gastrin, calcium-phosphorus product, and uremic gastropathy in cats with chronic kidney disease. *J Vet Intern Med* 2014; 28(3):827-837.

[11] Kuwahara Y, Ohba Y, Kitoh K, et al. Association of laboratory data and death within one month in cats with chronic renal failure. *J Small Anim Pract* 2006; 47(8):446-450.

[12] Chakrabarti S, Syme HM, Elliott J. Clinicopathological variables predicting progression of azotemia in cats with chronic kidney disease. *J Vet Intern Med* 2012; 26(2):275-281.

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Rough Anesthetic Recoveries

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Midwestern University
Glendale, Arizona

Anesthetic recovery is a critical part of the anesthesia process.[1-3] During the recovery period, the effects of anesthetic agents may still be present, and the patient may not have regained full consciousness and can react abruptly and unexpectedly. Therefore, the postanesthetic period requires attentive monitoring. It is also imperative that an appropriate perioperative plan be developed to minimize the risk for a rough recovery and/or to allow for timely intervention before patients accidently cause injury to themselves or those around them.

Patient- and anesthesia-related factors can cause a rough recovery, and understanding common contributing factors can help determine the most likely diagnosis and best treatment plan.* Although it can be difficult to differentiate pain from other behaviors (eg, anxiety, stress, dysphoria)—as many of the physiologic responses are similar[4-7]—assessment of behavior prior to administering any agents, use of multidimensional pain scales, and knowledge of drug effects and duration of action can help facilitate correct interpretation of behaviors displayed in the postanesthetic period.

The common causes of rough recoveries in dogs and cats discussed in this article are emergence delirium, pain, anxiety, bladder distension, opioid dysphoria, and benzodiazepine disinhibition.[4-6,8,9] Clinical signs are often similar regardless of the actual cause. Therefore, methodical assessment of the patient, as well as knowledge of when clinical signs started, drugs were administered, and patient pain level can help identify the most likely etiology of the rough recovery (see ***Rough Recovery Guidelines***).

*Drug dosages in this article are suggestions. Individual patients should be assessed to establish whether lower or higher doses are required based on adverse effects and patient status. Adequacy of the chosen drug should also be determined.

Emergence Delirium

Emergence delirium is a state of mental confusion and psychomotor agitation marked by hyperexcitability, restlessness, uncontrolled thrashing, and vocalization. Patients do not interact with humans and are unaware of their environment.[7,10] Signs are abrupt and usually occur following rapid emergence from anesthesia when the patient has not yet regained complete consciousness. The etiology is unclear, but early anesthesia arousal following use of short-acting inhalation anesthetics may be a contributing factor.[6,10,11]

Timing of clinical signs can help differentiate emergence delirium from other causes of a rough recovery. Emergence delirium occurs in the immediate recovery period, typically soon after inhalant anesthesia is discontinued. Patients may thrash uncontrollably and require rapid intervention to prevent injury. Administration of a small dose of an induction agent such as propofol (0.5-1 mg/kg slow IV; cats and dogs) is recommended.[7] Propofol is commonly used due to its fast onset and short duration of action but should be administered slowly until clinical signs subside. Excessive and

ROUGH RECOVERY GUIDELINES

Fast action is crucial if recovery is rough and may cause harm. However, if there is time, the patient should be assessed and the cause of the rough recovery identified prior to administration of any medication. Following are some treatment options for common causes of rough recovery.

Emergence Delirium

- Small dose of induction agent
- Propofol (0.5-1 mg/kg slow IV; cats and dogs)
  - Stopped when clinical signs subside

Pain

It should be determined how painful the procedure was and whether the patient needs additional analgesia (based on patient response), as well as when the last dose of analgesic was given and the drug's duration of action. Not all patients with rough recovery that vocalize are painful. A pain scale should be used to determine a pain score, as pain assessment can help determine whether analgesia is needed.

- Analgesics (ie, opioids, NSAIDs) are needed with a high pain score or when the patient is being assessed and it is not clear whether the patient is in pain.

Anxiety, Fear, & Aggression

Based on assessment of the patient's temperament prior to anesthesia, extra sedation may be needed. If this is the case, one of the following drugs (if there are no contraindications) can be administered and the patient reassessed:

- Low-dose acepromazine (0.01 mg/kg IV; cats and dogs)
- Low-dose dexmedetomidine (0.001 mg/kg IV; cats and dogs)

Bladder Distension

The bladder should be expressed or the patient walked if possible.

Opioid Dysphoria

- Butorphanol (0.1 mg/kg IV or IM; cats and dogs)
- Naloxone (0.005-0.01 mg/kg slow IV; cats and dogs), diluted prior to administration. The usual concentration is 0.4 mg/mL, which should be diluted to obtain a new concentration of 0.04 mg/mL (eg, 1 mL of undiluted naloxone and 9 mL of saline). Recommended rate of administration of the dilution is 0.5-1 mL/40 seconds. Administration should be stopped when clinical signs subside.
  - Naloxone administered too fast or at a dose that is too large can reverse analgesia and cause the patient to become painful. A rescue analgesic protocol should be prepared ahead of time.
  - Careful monitoring is needed, and readministration may be warranted if signs return.

Benzodiazepine (ie, Midazolam/Diazepam) Disinhibition

- Flumazenil (0.01 mg/kg slow IV; cats and dogs)
  - Stopped when clinical signs subside

fast administration should be avoided to reduce the risk for apnea and hypotension due to vasodilation.

Pain

Clinical signs of pain include vocalization, restlessness, hyperventilation or panting, and aggression, especially when painful areas are touched.[12,13]

Pain can be diagnosed using a pain scale (eg, short-form Glasgow Composite Measure Pain Scale, Colorado State University Acute Pain Scale).[12,14] Knowledge of the analgesic protocol used, duration of action, and time of administration can also help reach a diagnosis. An analgesic trial with opioids (eg, methadone or hydromorphone [0.1 mg/kg IV], buprenorphine [0.02 mg/kg IV]; cats and dogs) or other analgesic agents (eg, ketamine [0.6 mg/kg/hour CRI; cats and dogs]; NSAIDs) should be instituted and the patient reassessed if there is uncertainty on whether the patient is still painful.

Anxiety, Fear, & Aggression

Anxiety is the uncertainty and fear that result from anticipation of a real or imaginary threat and often impairs physical and psychological functioning. Clinical signs include vocalization, panting, and restlessness.[15]

Patients in which adequate pain management has been implemented but persistent vocalization and restlessness continues may be experiencing fear, stress, and/or anxiety. Administration of a tranquilizer or sedative (eg, acepromazine [0.01 mg/kg IV], dexmedetomidine [0.001 mg/kg IV]; cats and dogs) can be considered if there are no contraindications (eg, previous allergic reaction to the agent, patient is hypovolemic)[4,7]; however, some dogs and cats may only have a temporary response. In these cases, especially if restlessness is due to anxiety, agents such as trazodone (3-10 mg/kg PO) or gabapentin (10-25 mg/kg PO) can be administered. The patient will need to be reassessed after initial treatment, as some patients may require higher doses of these agents. The aim, however, should be to administer the lowest dose possible to minimize the risk for adverse effects while still achieving the desired outcome. Trazodone enhances calmness, reduces anxiety, and produces mild sedation with no apparent relevant adverse effects in dogs.[16,17]

Patients that are anxious may respond to being held, but this is not always feasible. Nonpharmacologic alternatives include anxiety or pressure wraps (eg, a thunder jacket) that maintain swaddling pressure and acupressure aimed to induce calmness.[18,19]

Bladder Distension

Bladder-distension–related discomfort may result in vocalization, restlessness, tachycardia, and/or panting.[4,5,20] The bladder should be palpated and expressed prior to recovery.

During the postanesthetic period, if there are signs of discomfort and restlessness, bladder size and turgidity should be reassessed and the bladder gently expressed if it is distended—this may minimize discomfort.[5] Ambulatory patients should be walked.

Opioid Dysphoria

Opioids, especially μ agonists (eg, hydromorphone, fentanyl), can result in dysphoric recoveries marked by vocalization, restlessness, hyperthermia, panting, and/or lack of response to human contact.[4,8] Opioid-related dysphoria is often a diagnosis of exclusion made after pain and bladder distension are ruled out and in patients with no response following administration of sedatives and tranquilizers. In these cases, μ-agonist–opioid administration worsens clinical signs. This highlights the importance of accurate pain assessment prior to administering these agents.

Butorphanol is a κ-agonist, μ-antagonist opioid that can reverse the adverse effects of μ-agonist opioids[21] and provide mild analgesia. Naloxone is the actual reversal agent and results in rapid resolution of adverse effects[10,21]; however, this drug has the potential to reverse the analgesic properties of the opioid. To decrease the risk for reversing analgesia, naloxone (0.005-0.01 mg/kg; cats and dogs) should

be diluted (see ***Rough Recovery Guidelines***, page 91) to allow for slow IV administration (0.5-1 mL/40 seconds) and stopped when signs subside. A rescue analgesic protocol should always be prepared ahead of time, and the patient should be pain scored. Clinical signs that stop after reversal confirms the diagnosis of opioid dysphoria.

Benzodiazepine Disinhibition

Benzodiazepine disinhibition is a paradoxical response that follows administration of these sedatives (eg, diazepam, midazolam); this reaction is often observed in healthy dogs and cats. Signs may be seen immediately after administration and/or during the recovery period and include vocalization, hyperexcitability, ataxia, drooling, nystagmus, aggression, and sudden attempts to eat the fluid line and bandages.[22,23] A higher incidence of disinhibition occurs in healthy patients but the etiology is not completely understood.[24,25]

Benzodiazepine disinhibition is often a diagnosis of exclusion that is made when the patient fails to respond to analgesics, sedatives, and tranquilizers. Flumazenil (0.01 mg/kg slow IV; cats and dogs) is the reversal agent and results in rapid cessation of clinical signs,[25,26] confirming the diagnosis of benzodiazepine disinhibition.

Prognosis & Prevention

Reviewing patient history and medical records of previous sedation and anesthetic recoveries before medication is administered can help prevent a rough recovery. It is also important to properly record any rough recovery, treatment provided, and responses to treatment. Knowledge of previously noted complications can help clinician's anticipate potential future issues and implement pre-emptive strategies. Strategies may include modification of the anesthetic protocol and administration of preanesthetic drugs at home[27] and/or in the clinic. For example, a cat that previously experienced benzodiazepine-induced disinhibition on recovery should receive a different premedication protocol, or a dog with a known history of opioid-related dysphoria can often be managed with opioid-minimal/opioid-free protocols, emphasizing locoregional analgesia, NSAIDs, and CRIs of nonopioid drugs (eg, lidocaine, dexmedetomidine, ketamine). Consultation with a board-certified specialist in veterinary anesthesia and analgesia can be helpful in these cases.

Using a pain scoring scale prior to starting the procedure and prior to drug administration can help during the recovery period—for example, this can aid in differentiating whether vocalization is due to pain or anxiety. An adequate analgesic protocol is also a key component for optimal perioperative management and return to normal physiologic function. Some agents may need to be readministered depending on the procedure, patient response, type of analgesic used, time of drug administration, and duration of action of each drug. Suboptimal use of analgesics, but also unnecessary administration of drugs (eg, opioids) to nonpainful patients, can result in a rough recovery.

Conclusion

To correctly diagnose a rough anesthetic recovery, it is important to anticipate and reduce pain, anxiety, and fear (using pharmacologic and/or nonpharmacologic methods), as well as to understand the temperament of the patient, procedure, medications, and possible drug interactions. Knowledge of common causes of rough recoveries and appropriate treatment can aid in optimization of the recovery period.

A rescue analgesic protocol should always be prepared ahead of time, and the patient should be pain scored.

See page 73 for references.

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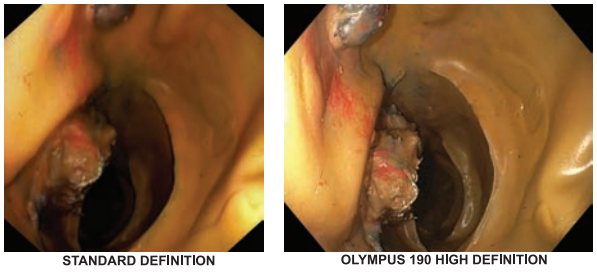

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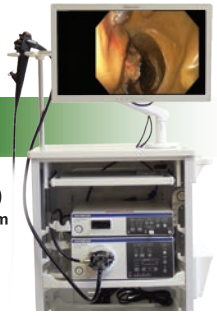

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QUIZ CORNER

QUIZ YOURSELF

on this issue's features

Quiz Corner is offered by the publisher for entertainment purposes only and does not apply toward CE credit. Questions are provided by editorial staff and are not subject to peer review.

1 **CONSULT THE EXPERT** **PAGE 19**

Which of the following is a benign process that occurs in most dogs after TPLO that may sometimes result in pain and lameness?

A. Surgical site infection
B. Patellar thickening
C. Residual instability
D. Plateau rock-back

2 **DIAGNOSTIC/MANAGEMENT TREE** **PAGE 26**

Which of the following tests for leptospirosis can be performed on a urine sample?

A. PCR
B. LipL-32 ELISA
C. Microscopic agglutination test
D. None of the above

3 **PROCEDURES PRO** **PAGE 74**

Feline orthopedic examination should begin at the _____.

A. Head
B. Lumbar spine
C. Proximal aspect of the limbs
D. Distal aspect of the limbs

4 **CASE IN POINT** **PAGE 83**

During the treatment period for post-traumatic stress disorder, pet owners should do which of the following?

A. Scold the dog if it reacts to a trigger situation
B. Ignore the dog if it reacts to a trigger situation
C. Attempt to avoid triggering situations
D. Re-enact triggering situations

5 **CONSULT THE EXPERT** **PAGE 90**

A rough anesthetic recovery that occurs in the immediate recovery period is most likely due to _____.

A. Bladder distention
B. Opioid dysphoria
C. Benzodiazepine disinhibition
D. Emergence delirium

Answer Key:
1: B 2: A 3: D 4: C 5: D

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