January/February 2023

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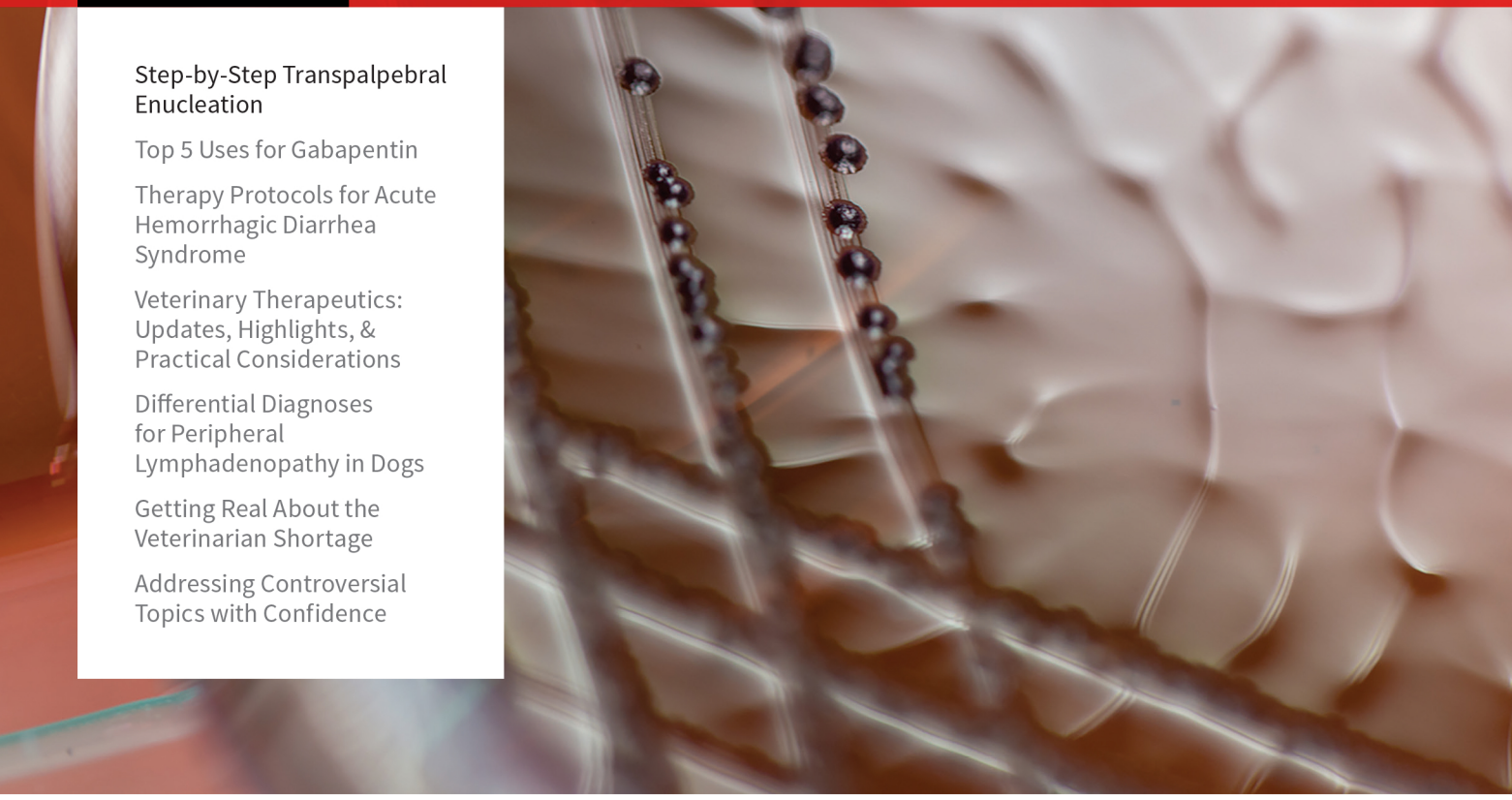
PATHOGEN PROFILE: *ESCHERICHIA COLI*

IN THIS ISSUE



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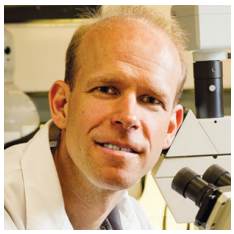

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Providing small animal practitioners and their teams with practical, relevant information on the latest topics in veterinary medicine

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Zorbium™ Ⓒ Ⓘ

[buprenorphine transdermal solution]

For use in cats only

20 mg/mL

For topical application in cats

Opioid analgesic

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

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

HUMAN SAFETY WARNING

Abuse Potential

ZORBIUM contains buprenorphine, an opioid that exposes humans to risks of misuse, abuse, and addiction, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of ZORBIUM. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drugs or alcohol) or mental illness (e.g. depression).

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ZORBIUM. Monitor for respiratory depression if human exposure to buprenorphine occurs. Misuse or abuse of buprenorphine by swallowing, snorting, or injecting poses a significant risk of overdose and death.

Accidental Exposure

Because of the potential for adverse reactions associated with accidental exposure, ZORBIUM should only be administered by veterinarians or veterinary technicians who are trained in the handling of potent opioids. Accidental exposure to even one tube of ZORBIUM, especially in children, can result in a fatal overdose of buprenorphine.

Risks From Concurrent Misuse or Abuse with Benzodiazepines or Other CNS Depressants

Concurrent misuse or abuse of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

See Human Safety Warnings for detailed information.

INDICATION:

ZORBIUM is indicated for the control of postoperative pain associated with surgical procedures in cats.

DOSAGE AND ADMINISTRATION:

This product should only be administered by veterinary personnel.

ZORBIUM is for administration only once for the surgical procedure. ZORBIUM should be applied 1 to 2 hours before surgery. A single application provides analgesia for 4 days. ZORBIUM should only be applied topically to the dorsal cervical area at the base of the skull. Do not apply if dorsal cervical skin is diseased or injured. The dosage of ZORBIUM is 1.2 – 3.1 mg/lb (2.7 – 6.7 mg/kg) administered topically as the entire tube contents according to the following dosing table:

Pounds of Body Weight	Kilograms of Body Weight	Dose of ZORBIUM
2.6 to 6.6	1.2 to 3	0.4 mL (8 mg) pink tube
>6.6 to 16.5	>3 to 7.5	1 mL (20 mg) green tube

Dose Application

Wear impermeable latex or nitrile gloves, protective glasses, and a laboratory coat to prevent direct solution contact with human skin, eyes, or mucosa when handling and applying the solution. Do not dispense ZORBIUM for administration at home by the pet owner (see HUMAN SAFETY WARNINGS).

See product insert for complete dosing and administration information.

CONTRAINDICATIONS:

ZORBIUM is contraindicated in cats with known hypersensitivity to buprenorphine hydrochloride, any of the inactive ingredients of ZORBIUM, or known intolerance to opioids.

WARNINGS:

HUMAN SAFETY WARNINGS:

Not for use in humans. Keep this and all medications out of reach of children and pets.

Human User Safety While Handling ZORBIUM in the Hospital:

Protective Covering: Do not come into direct contact with ZORBIUM. Wear impermeable latex or nitrile gloves, protective glasses, and a laboratory coat when applying ZORBIUM.

Mucous Membrane or Eye Contact During Application:

Direct contact of ZORBIUM with the eyes, oral, or other mucous membranes could result in absorption of buprenorphine and the potential for adverse reactions. If accidental eye, oral, or other mucous membrane contact is made during application, flush the area with water and contact a physician immediately. If wearing contact lenses, flush the eye first and then remove the contact lens.

Skin Contact During Application:

Following application to the cat, allow a minimum drying time of 30 minutes before direct contact with the application site. If human skin is accidentally exposed to ZORBIUM, wash the exposed area immediately with soap and water and contact a physician. Accidental exposure could result in absorption of buprenorphine and the potential for adverse reactions.

Drug Abuse, Addiction, and Diversion of Opioids:

Controlled Substance:

ZORBIUM contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids.

Abuse:

ZORBIUM contains buprenorphine, an opioid substance, that can be abused and is subject to misuse, abuse, and addiction, which may lead to overdose and death. This risk is increased with concurrent use of alcohol and other central nervous system depressants, including other opioids and benzodiazepines.

ZORBIUM should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.

Prescription drug abuse is the intentional, non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse.

Storage and Disposal:

ZORBIUM is a Schedule III opioid. Store in a locked cabinet according to federal and state controlled substance requirements/guidelines. Any unused or expired tubes must be destroyed by a reverse distributor; for further information, contact your local DEA field office or call Elanco US Inc. at 1-888-545-5973.

Information for Physician:

ZORBIUM transdermal solution contains a mu opioid partial agonist (20 mg buprenorphine/mL). In the case of an emergency, provide the physician with this package insert. Naloxone may not be effective in reversing respiratory depression produced by buprenorphine. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride has also been used as a respiratory stimulant.

ANIMAL SAFETY WARNINGS:

For topical use in cats only. **This product should only be administered by veterinary personnel.**

Do not apply ZORBIUM if the application site at the dorsal cervical area has diseased or injured skin.

Do not apply ZORBIUM to anatomic areas other than the dorsal cervical area because absorption characteristics may be different.

PRECAUTIONS:

Following anesthesia and opioid analgesia, body temperature should be monitored postoperatively for immediate hypothermia and subsequent hyperthermia. Hyperthermia can occur and persist after the hypothermic effects of anesthesia have resolved.

The safe use of ZORBIUM has not been evaluated in debilitated cats or cats with renal, hepatic, cardiac, or respiratory disease.

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

The safe use of ZORBIUM has not been evaluated in cats younger than four months old.

The safe use of ZORBIUM has not been evaluated in cats weighing less than 2.6 pounds or more than 16.5 pounds.

ADVERSE REACTIONS:

In a randomized, multi-centered, double-masked, field study, ZORBIUM™ (buprenorphine transdermal solution) (N=113) or vehicle control (N=109) was administered to cats prior to elective surgical reproductive sterilization (castration/ovariohysterectomy) in conjunction with forelimb onychectomy. Cats enrolled in the study were 4 months to 5 years of age and weighed 1.1 to 5.7 kg (2.5 to 12.5 lb). Clinical observations and physiological parameters were monitored prior to, during, and after surgery for 96 hours after sternal recumbency. Supplemental heat and fluids were allowed. There were no deaths during the study and no cats received an opioid reversal agent. Three ZORBIUM and 2 vehicle control cats were removed due to hyperthermia suspected to be treatment related. One ZORBIUM cat was removed due to fractious behavior 30 minutes following surgery. Adverse reactions were defined as any single excursion outside the normal range, as defined: 100.5 – 102.5 °F body temperature; 60 – 120 mmHg mean arterial pressure; 88 – 180 beats per minute for heart rate; 24 – 44 breaths per minute for respiratory rate. A summary of adverse reactions during anesthesia (from anesthetic induction through recovery defined as sternal recumbency) is provided in Table 1.

Table 1. Adverse Reactions During Anesthesia:

Adverse Reaction*	ZORBIUM (N=113)	Vehicle Control (N=109)
Hypothermia	37 (32.7%)	29 (26.6%)
Hypotension	31 (27.4%)	28 (25.7%)
Hypertension	27 (23.9%)	18 (16.5%)
Tachycardia	14 (12.4%)	14 (12.8%)
Sedation	12 (10.6%)	7 (6.4%)
Oxygen saturation ≤ 90%	6 (5.3%)	2 (1.8%)
Bradycardia	4 (3.5%)	2 (1.8%)
Hyperthermia	3 (2.7%)	4 (3.7%)

*Physiological adverse reactions were defined as any single excursion outside the normal range at any 10 minute interval during the entire duration of anesthesia.

After recovery, cats were observed in the hospital and underwent physiological assessments that included indirect mean arterial blood pressure, heart rate, respiratory rate, body temperature, lung auscultation, heart auscultation, and assessments of urination, defecation, and appetite. A summary of adverse reactions after anesthetic recovery (sternal recumbency) in all cats is reported in Table 2.

Table 2. Adverse Reactions After Anesthetic Recovery:

Adverse Reaction*	ZORBIUM (N=113)	Vehicle Control (N=109)
Hypothermia	107 (94.7%)	105 (96.3%)
Hyperthermia	84 (74.3%)	62 (56.9%)
Sedation	64 (56.6%)	48 (44.0%)
Tachypnea	56 (49.6%)	70 (64.2%)
Hypotension	50 (44.2%)	51 (46.8%)
Hypertension	42 (37.2%)	34 (31.2%)
Bradycardia	34 (30.1%)	45 (41.3%)
Tachycardia	32 (28.3%)	39 (35.8%)
Anorexia	25 (22.1%)	32 (29.4%)
Dysphoria	20 (17.7%)	29 (26.6%)
Diarrhea	11 (9.7%)	11 (10.1%)
Bradypnea	11 (9.7%)	7 (6.4%)
Leukocytosis	6 (5.3%)	4 (3.7%)
Hyperactivity	2 (1.8%)	9 (8.3%)

*Physiological adverse reactions were defined as any single excursion outside the normal range following anesthetic recovery (sternal recumbency) through 4 days postoperatively.

Hyperthermia was the only adverse event observed in more than 10% of cats in the ZORBIUM group after the day of surgery (24 – 96 hours). The percentage of cats in the ZORBIUM group with hyperthermia decreased over time from 66.4% on Day 0 to 28.3% on Day 1, and to 6.2% by Day 4. A summary of adverse reactions (from anesthetic recovery through 96 hours after recovery) in cats in the ZORBIUM group by study day is reported in Table 3.

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A MATTER OF OPINION PAGE 30

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PROCEDURES PRO PAGE 15

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PROCEDURES PRO PAGE 15

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DIFFERENTIAL DIAGNOSIS PAGE 54

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CASE ROUTES PAGE 59

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PATHOGEN PROFILE PAGE 55

Table 3. Adverse Reactions in ZORBIUM Cats (N=113) by Day:

Adverse Reaction*	Day 0	Day 1	Day 2	Day 3	Day 4
Hypothermia	106 (93.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
Hyperthermia	75 (66.4%)	32 (28.3%)	18 (15.9%)	14 (12.4%)	7 (6.2%)
Sedation	64 (56.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachypnea	51 (45.1%)	5 (4.4%)	2 (1.8%)	3 (2.7%)	4 (3.5%)
Hypotension	42 (37.2%)	2 (1.8%)	1 (0.9%)	4 (3.5%)	2 (1.8%)
Hypertension	28 (24.8%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Anorexia	25 (22.1%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Bradycardia	24 (21.2%)	3 (2.7%)	2 (1.8%)	3 (2.7%)	5 (4.4%)
Tachycardia	24 (21.2%)	4 (3.5%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Dysphoria	20 (17.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bradypnea	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperactivity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

*Physiological adverse reactions were defined as any single excursion outside the normal range following anesthetic recovery (sternal recumbency) through 96 hours postoperatively.

CONTACT INFORMATION:

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 reporting adverse drug experience for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

EFFECTIVENESS:

The effectiveness of ZORBIUM was demonstrated in cats that underwent elective reproductive sterilization in conjunction with forelimb onychectomy surgery in a randomized, multi-centered, double-masked, vehicle-controlled, field study across 12 investigative sites. Enrolled cats were between 4 months to 5 years of age and weighed 2.5 to 12.5 pounds (1.1 – 5.7 kg).

Cats in the ZORBIUM group received a single dose of 8 mg or 20 mg of buprenorphine according to body weight (see DOSAGE AND ADMINISTRATION). Cats in the vehicle control group received a transdermal solution of 50 mg/mL padimate O in ethanol. The dose was administered topically onto the dorsal cervical skin 1 – 2 hours prior to anesthetic induction for surgery. For intraoperative analgesia, all cats in the study received a single intramuscular injection of an alpha$_2$-agonist 30 minutes prior to anesthetic induction, and a 4-point metacarpal ring block with lidocaine after induction. The adequacy of pain control was scored through 96 hours after surgery. If pain control was considered inadequate at any time following treatment, rescue analgesia was provided immediately. Treatment success was defined as a cat that did not require rescue analgesia, need opioid reversal, or experience an adverse event suspected to be related to treatment through the entire 96-hour post-recovery period. A cat was considered a treatment failure if it had inadequate pain control, required opioid reversal, or experienced an adverse event suspected to be related to treatment.

A total of 19 ZORBIUM and 63 vehicle control cats were removed from the study due to inadequate pain control. Most of these failures occurred on the day of surgery in both groups; however, there were 4 ZORBIUM group cats and 5 vehicle control cats removed due to inadequate pain control between 1 and 3 days after surgery.

Effectiveness was evaluated in 219 cats (112 in the ZORBIUM group and 107 cats in the vehicle control group), and field safety was evaluated in 222 cats (113 cats in the ZORBIUM group and 109 cats in the vehicle control group). Of the 112 cats in the ZORBIUM group, 89 were treatment successes; of the 107 vehicle control cats, 42 were treatment successes. Comparison of the ZORBIUM group and the vehicle control group demonstrated a statistically significant difference in the treatment success rates ($p = 0.0003$).

Hypothermia was common in both groups during surgery. The overall mean postoperative body temperature was higher in the ZORBIUM group than in the vehicle control group. Mean postoperative body temperatures in the ZORBIUM group were above the normal range at 4 and 8 hours postoperatively (mean±SD of 102.7°±1.2 °F and 102.6°±1.0 °F, respectively [normal range: 100.5 – 102.5 °F]). Mean indirect arterial blood pressure (MAP) was similar between the 2 treatment groups over time. Urination, defecation, appetite, and daily body weights after surgery were not affected by ZORBIUM administration. Fifteen cats in the ZORBIUM group had an increased fibrinogen at discharge, compared to 2 cats in the vehicle control group.

Fluid administration (intravenous and subcutaneous) and supplemental heat support after surgery were the most common concurrent treatments and were used similarly in both groups.

TARGET ANIMAL SAFETY:

Twelve Day Target Animal Safety Study: In a 12-day laboratory study, ZORBIUM was administered to 32 healthy four-month-old domestic cats (8 cats per group) at 0 mg/kg (vehicle control), 6.7 mg/kg (1X), 13.3 mg/kg (2X), and 20 mg/kg (3X) as a topical application to the dorsal cervical area every 4 days for a total of 3 doses. Dose-independent euphoria, mild dysphoria, and mydriasis were observed after ZORBIUM administration. Maximum scores (for euphoria, dysphoria, and mydriasis) in the ZORBIUM groups reached 3 (mildly dysphoric) between 1 – 2 hours after the first dose. On the other 2 dosing days (Days 4 and 8), maximum scores were 2 (euphoric). Euphoria in some cats persisted from 36 to 72 hours.

On dosing day 1, mydriasis was observed in approximately half the cats administered ZORBIUM by 24 hours after dosing (peaked in all ZORBIUM groups at 8 hours) and was not observed between 48 – 93 hours. After the day 8 dose (third dose), it was rarely observed (1 cat in 1X group; 2 cats in 3X at 48 hours; 1 cat in 2X at 72 hours).

Cats administered ZORBIUM had higher body temperatures compared to the vehicle control group throughout the study. Following the initial dose, the mean temperatures in cats administered ZORBIUM increased above normal and were up to 1.8 ºF greater than the vehicle control group. Increased body temperature primarily occurred during the first 8 hours after the initial dose and was observed in the majority of cats administered ZORBIUM. Elevated temperatures ranged from 102.6 °F to 104.5 °F. The highest temperatures occurred at 2 hours after the first dose, gradually decreasing by 24 hours. By 3 days after dose administration, body temperatures in cats administered ZORBIUM had returned to levels observed in the vehicle control group. After the second and third doses (days 4 and 8), mean temperatures in all ZORBIUM groups were again higher than in the vehicle control group, but not higher than the normal reference range.

Constipation was recorded for 20 cats (1 vehicle control; 3 in 1X; 4 in 2X; 6 in 3X groups) after the first dose. The constipation was mild and transient. Three cats (2 in the 1X group and 1 in the 3X group) were administered a laxative. ZORBIUM had no clinically significant effects on heart rate or respiratory rate. There were no clinically relevant changes to serum chemistry, hematology, or urinalysis outcomes. Histopathology evaluations revealed mild inflammation of skin at the application site.

Seven Day Target Animal Safety Study: In a 7-day laboratory study, ZORBIUM was administered once topically to the dorsal cervical area of 24 healthy adult domestic cats (6 cats/group) at 0 mg/kg (0X; vehicle control), 3.3 (0.5X), 10 (1.5X), or 30 mg/kg (4.5X the maximal dose of 6.7 mg/kg). Cats were observed for 7 days after the single dose. Clinical results were similar to the 12-day margin of safety study, even at the higher dose of 30 mg/kg, except for transient increases in heart rate in the ZORBIUM groups compared to the vehicle control group. Mean heart rates in ZORBIUM groups were higher than in the vehicle control group from 2 hours through approximately 48 hours after dose administration. Tachycardia (>240 beats per minute) occurred in two cats in the 0.5X group and two cats in the 4.5X group for at least one timepoint after dose administration. The highest heart rate was 260 (in the 0.5X group) and no dose relationship was evident. Dose-independent euphoria, mild dysphoria, and mydriasis were noted in the ZORBIUM groups. Mild constipation and/or abdominal distension were observed with ZORBIUM administration. Transient increases in plasma chloride and sodium concentrations in the ZORBIUM groups compared to vehicle control group indicated mild dehydration.

Cardiovascular Safety Study: In a 12-day cardiovascular laboratory safety study, ZORBIUM was administered to 8 healthy adult cats (4 cats per group) at 0 mg/kg (vehicle control) and 6.7 mg/kg (1X) as a topical application to the dorsal cervical region every 4 days for a total of 3 doses. Continuous, direct physiological monitoring (telemetry) was conducted from 2 hours prior to the first dose through 4 days following the third (final) dose. Body temperature increases averaged <0.4 ºF in ZORBIUM group cats over vehicle control cats. In the vehicle control group, 102.6 °F was the maximum temperature, observed at 93 hours after the first dose. In the ZORBIUM group, 103.4 °F was the maximum temperature, observed at 20 hours after the first dose. Heart rate (HR) increased an average of 15.2 beats/minute in the ZORBIUM group cats compared to vehicle control cats. The maximum heart rate in the ZORBIUM group reached 231 beats/minute. In the vehicle control group, the maximum heart rate was 219 beats/minute. Blood pressure (arterial systolic, diastolic, and mean) in the ZORBIUM group cats was not significantly different from the vehicle control cats. There were no clinically significant effects of ZORBIUM on qualitative electrocardiogram results.

STORAGE INFORMATION:

Store at or below 25 °C (77 °F). Excursions permitted to 30 °C (86 °F).

HOW SUPPLIED:

ZORBIUM is available in applicator tubes that deliver a dose volume of 0.4 mL or 1 mL (20 mg/mL buprenorphine) in multi-packs of 10 tubes.

Approved by FDA under NADA # 141-547

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140 USA

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- **No need to administer repeat injections or dispense buprenorphine during the critical first few days after surgery**

Indication: Zorbium is indicated for the control of postoperative pain associated with surgical procedures in cats.

Important Safety Information: **Before using ZORBIUM (buprenorphine transdermal solution), read the entire package insert including the Boxed Human Warning. Call 1-888-545-5973 for full prescribing information. ZORBIUM contains buprenorphine, an opioid that exposes humans to risks of misuse, abuse, and addiction, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of ZORBIUM. Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ZORBIUM. ZORBIUM should only be administered by veterinarians or veterinarian technicians who are trained in the handling of potent opioids. Accidental exposure to even one tube of ZORBIUM, especially in children, can result in a fatal overdose.** ZORBIUM is for topical application in cats only. Following application to the cat, allow a minimum drying time of 30 minutes before direct contact with the application site. Do not administer to cats with a known hypersensitivity to buprenorphine hydrochloride, any inactive ingredients of ZORBIUM, or known intolerance to opioids. Most common adverse reactions during anesthesia were hypothermia, hypotension, and hypertension, and after anesthetic recovery were hypothermia, hyperthermia, and sedation. The safe use of ZORBIUM has not been evaluated in debilitated cats, those with renal, hepatic, cardiac or respiratory disease, pregnant lactating, breeding, in cats younger than four months old or <2.6 lbs or >16.5 lbs. Please see accompanying brief summary for additional product safety information.

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See pages 2 & 4 for product information summary.

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MERCK
Animal Health

IN THIS ISSUE

ON THE COVER

PATHOGEN PROFILE
***Escherichia coli* in Dogs & Cats**
J. Scott Weese, DVM, DVSc, DACVIM, FCAHS

PG 55

NOTICE OF CORRECTION
In the article "Drugs Used for Emesis Induction" published in the October 2022 issue of *Clinician's Brief*, the dexmedetomidine section has been updated to provide clarification regarding oral detomidine transmucosal gel.

A corrected version has been published online and can be found at **brief.vet/emesis_induction**

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INDICATIONS Adequan® Canine is recommended for intramuscular injection for the control of signs associated with non-infectious degenerative and/or traumatic arthritis of canine synovial joints. **IMPORTANT SAFETY INFORMATION** Adequan® Canine should not be used in dogs who are hypersensitive to PSGAG or who have a known or suspected bleeding disorder. It should be used with caution in dogs with renal or hepatic impairment. Adverse reactions in clinical studies (transient pain at injection site, transient diarrhea, and abnormal bleeding) were mild and self-limiting. In post approval experience, death has been reported in some cases; vomiting, anorexia, depression/lethargy and diarrhea have also been reported. The safe use of PSGAG in breeding, pregnant or lactating dogs has not been evaluated. **Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian. For additional safety information, **please see Full Prescribing Information at adequancanine.com**.

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1. Adequan® Canine Package Insert, Rev 1/19.

ON THE WEB

THIS MONTH'S FEATURED CLINICAL CONTENT AVAILABLE ONLY ONLINE

CONTINUING EDUCATION

Hospice & End-of-Life Care

This online CE course reviews end-of-life care practices, including navigating difficult conversations with pet owners, exploring alternative euthanasia methods, and providing palliative care when euthanasia is not an option.

brief.vet/hospice_care

WEB EXCLUSIVE

Top 5 Tips for Managing Nocturnal Anxiety in Geriatric Dogs

Julia Albright, DVM, MA, DACVB
Kevin Pflaum, DVM

brief.vet/managing_anxiety

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Getting Real About the Veterinarian Shortage

Many clinicians feel pushed to their limits in practice. Below and online, 3 clinicians discuss what it feels like to work in the veterinary industry right now.

In my opinion, a lot of practices think they need more doctors, when they actually need more support staff. Our support staff have an incredible amount of talent, training, and communication skills, but often they are limited to restraining patients and drawing blood. If we did a better job leveraging that talent, we might be better off.

I guess I am not convinced the entirety of the problem is a veterinarian shortage per se. Issues present in the industry for a long time came to the fore with COVID. It became more obvious where we had some shortcomings. I think that sped up the burnout for a lot of people in the field.
—Clinician in practice for 15 years

Practices that try to take on everything end up with more burnout and more staff turnover, which does not help patients. You cannot say *yes* to everything. There are only so many hours in a day. There is only so much you can do with the staff you have.

Practices that prioritize the mental health of staff and give them the ability to say *no* do better. Practices that realize [an individual] can only do so much and recognize they might not have enough staff to see some cases are able to set realistic expectations for clients.
—Clinician in practice for 13 years

Working in veterinary medicine is frustrating right now. I feel like I cannot accommodate my patients' needs. It seems like everyone is facing burnout in this profession, but what can really be done? These problems are outside my control. I keep reminding myself that I am only one person, and I only have so many hours in the day.

I still show up for work because I love my job. I love being a clinician. It is what I have always wanted to do. It is exactly what I always dreamed of doing. It is depressing when you are doing everything you can to help a patient and the patient's owner does not recognize you are working within certain limitations out of your control.
—Clinician in practice for 22 years

HAS A STAFFING SHORTAGE AFFECTED YOU?

Scan the QR code or use this link (**cliniciansbrief.com/article/veterinarian-shortage**) to read the rest of these interviews and share your experience in the comments.

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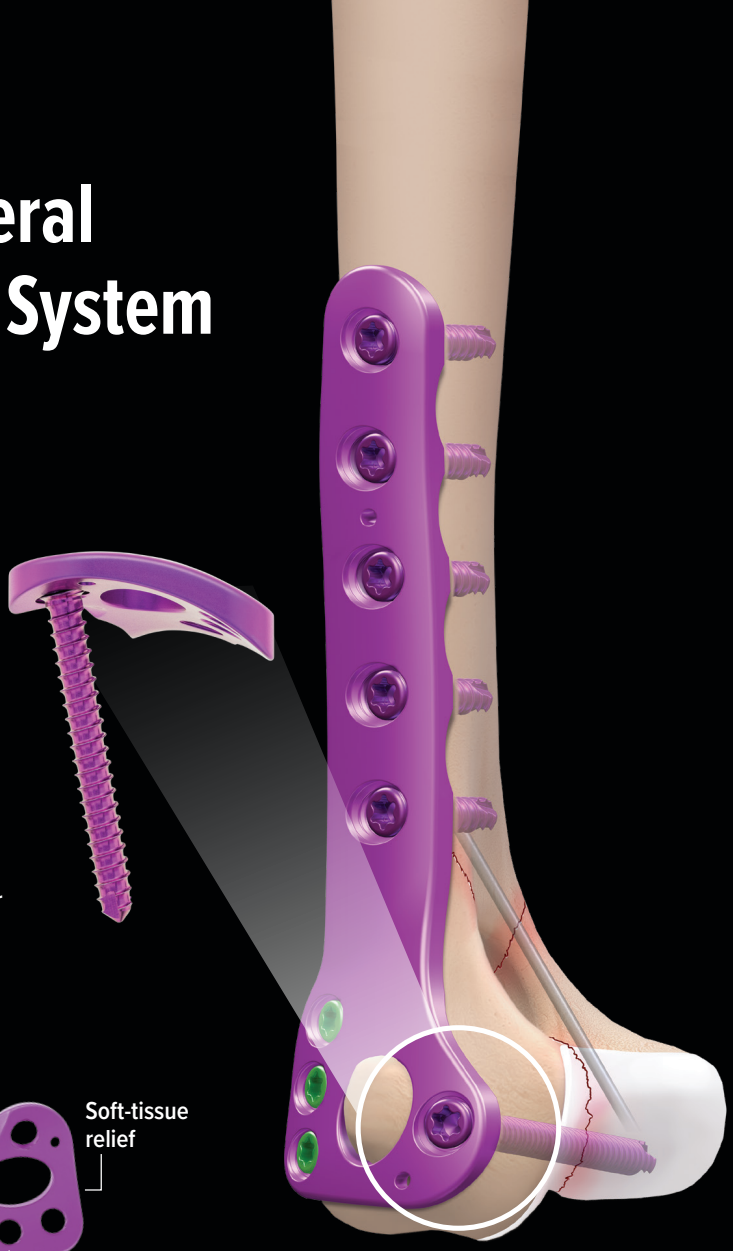

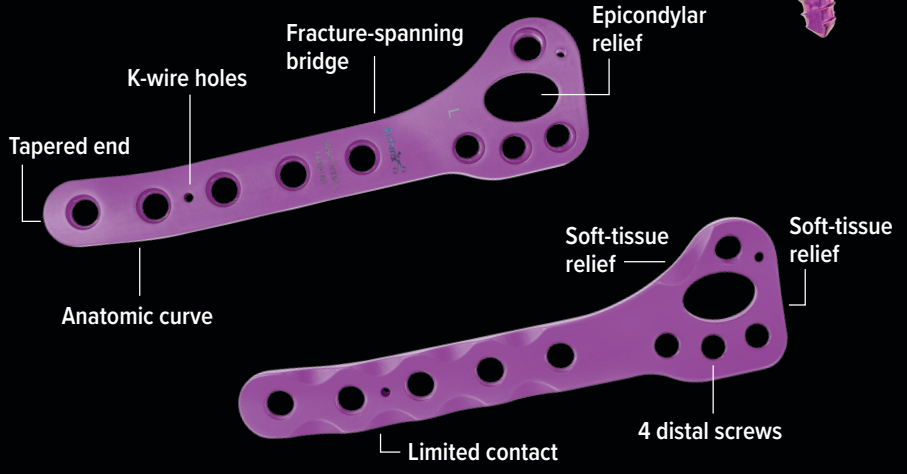

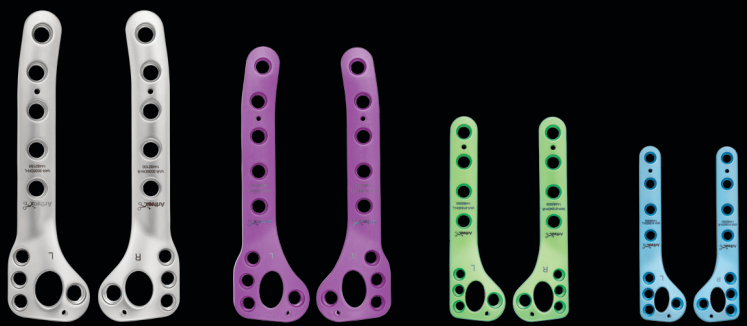

Scan for more information on the OrthoLine distal humeral fracture system

Arthrex® Vet Systems

ArthrexVetSystems.com

Reference

1. Arthrex, Inc. Data on file (APT 05162). Naples, FL; 2021.

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Addressing Controversial Topics with Confidence

"She replied that she had been doing research online …

… and I wanted to confidently convey my medical opinion."

Dear Second Opinion,

A recent wellness examination turned awkward when a long-time client asked for a diet recommendation for her healthy 2-year-old crossbreed dog. I suggested a chicken-based adult maintenance kibble made by a well-known pet food company. She replied that she had been doing research online and she no longer wants to feed commercial food made by any of the big pet food manufacturers. She explained that she plans to feed a homemade raw diet because it is *natural* and will better protect her pets from diseases they would likely develop on a commercial diet like the one I recommended. Not wanting to upset her or potentially lose a good client, I responded with something neutral and continued the examination.

Could I have handled this better? I do not want to lose a client, but I want to confidently convey my medical opinion over that of Dr. Google.
—Can't Compete with Dr. Google

Dear Can't Compete with Dr. Google,

Sometimes a client says things I do not agree with, and I am left wondering how to share my knowledge without creating barriers. You are definitely on the right track of being respectful, not wanting to lose a good client, and engaging in objective analysis of the situation. I have some suggestions on what you can do and what you should avoid doing in these situations ▪▪▪

Follow this link **cliniciansbrief.com/article/veterinary-misinformation** or scan the QR code below to read the advice from Sarah Wooten, DVM, CVJ, on how to handle these difficult conversations with pet owners.

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Transpalpebral Enucleation in Cats & Dogs

Kerry Gunsalus, DVM
DJ Haeussler, Jr, DVM, MS, DACVO
The Animal Eye Institute
Cincinnati, Ohio

Enucleation is recommended in patients with a blind and painful eye or an intraocular tumor that cannot be effectively resected using other methods. Conditions that can lead to enucleation include glaucoma, severe uveitis, ocular trauma, and perforated corneal ulcers. The primary goals of enucleation are removing a source of chronic pain, infection, and/or metastasis, as well as gathering diagnostic information regarding the contralateral eye and therefore patient systemic health.

Techniques

Multiple techniques for enucleation are available. It is important to consider the underlying disease process when choosing an approach.

Subconjunctival Approach

The most common technique is the subconjunctival approach, in which the globe is reached via dissection through the conjunctiva. The eyelid margins, conjunctiva, and third eyelid are then resected. This approach should not be used if there is obvious infection of the conjunctiva, neoplasia of the extraocular surface, or corneal perforation.

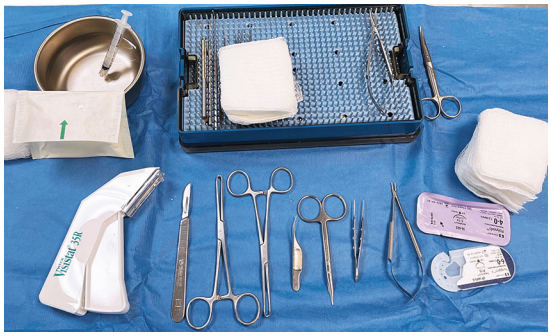
Transpalpebral Approach

With the transpalpebral approach, initial dissection is made through the eyelids, allowing removal of the globe and associated supportive and secretory tissues as one unit. This approach minimizes the risk for leaving residual conjunctival tissue (which can cause draining fistulas from the orbit) and is recommended for neoplasia or infection (as there is less risk for spread of ocular surface contaminants throughout the orbit). The transpalpebral approach is discussed in this article.

STEP-BY-STEP: TRANSPALPEBRAL ENUCLEATION

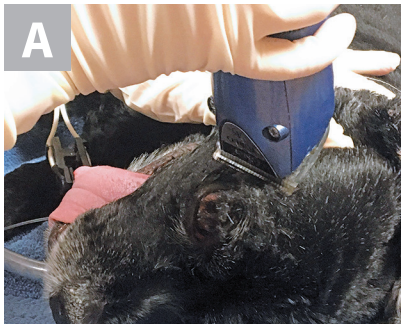
WHAT YOU WILL NEED

- Sterile drape
- Towel clamps
- Sterile gauze
- Surgical staples
- #10 scalpel blade and handle
- Allis tissue forceps
- Colibri forceps
- Stevens tenotomy scissors
- Bishop-Harmon forceps
- Barraquer needle holder
- 4-0 absorbable suture
- 6-0 nonabsorbable suture
- Absorbable gelatin sponge
- Sterile bowl
- Sterile saline
- 3-mL syringe
- Vacuum pillow



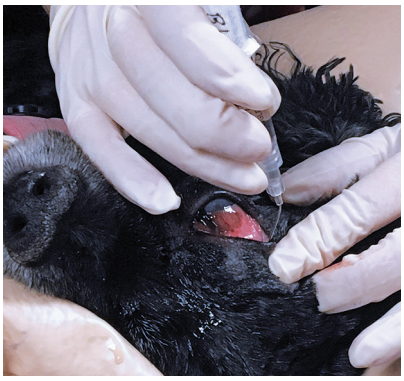
STEP 1

Place the patient in lateral recumbency with the surgical eye facing upward. Shave the eyelids (***A***), and prepare the periocular and ocular surface tissues with dilute povidone iodine (add povidone iodine [4 mL] to sodium chloride [1,000 mL]; ***B***). Contact time for irrigation of the globe and associated structures is ≈2 to 3 minutes. Position and support the head with a vacuum pillow (***C***). Perioperative cefazolin can be administered intravenously at this time.



Author Insight

A retrobulbar block may be performed with 2% lidocaine (2 mL) and/or 0.5% bupivacaine (2 mL) to provide intraoperative and postoperative analgesia. Before injection, the syringe plunger should be drawn back to check for aspirated blood to avoid inadvertent injection into a vessel. Acceptable approaches include the inferior–temporal palpebral and supratemporal routes (***Figure***). Alternative analgesia options include intraoperative bupivacaine splash blocks and intraorbital lidocaine–bupivacaine infused absorbable gelatin sponges.

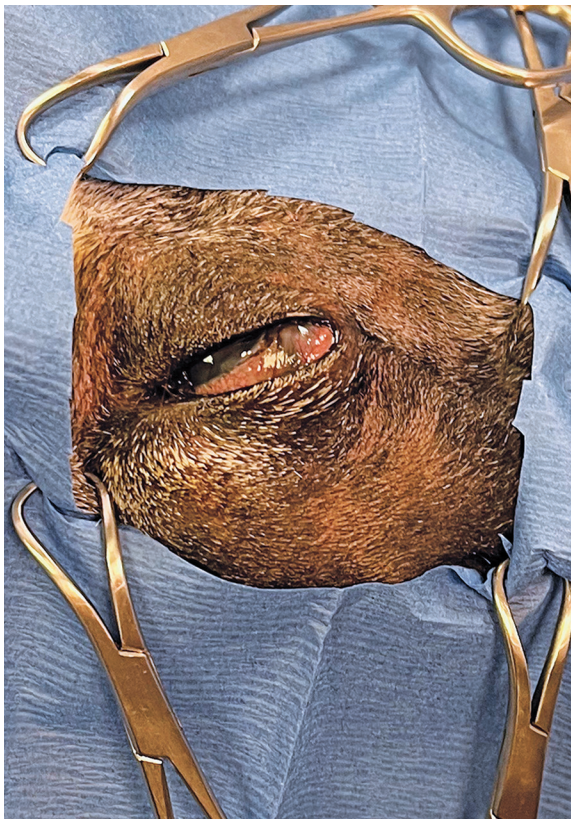


STEP 2

Reirrigate the eyelids with dilute povidone iodine, and drape the surgical site.

Author Insight

Surgical scrubs that contain detergents should be avoided. Periocular skin and ocular surface require presurgical prepping with sterile drape after povidone iodine has been used to clean the periocular and ocular surfaces.

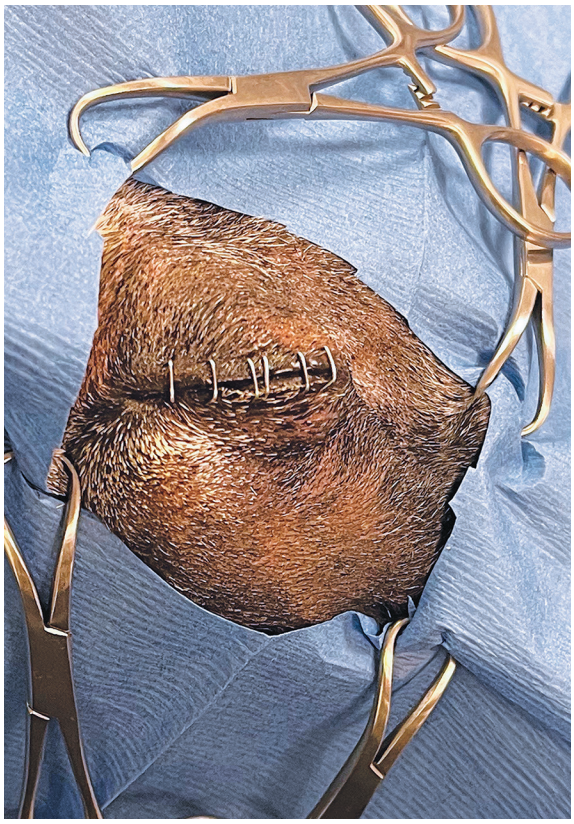


STEP 3

Suture the eyelids closed with an absorbable or non-absorbable suture in a continuous suture pattern.

Author Insight

Initial incisions should be no further than 2 mm from the eyelid margin, and caution should be used with wide bites of the suture to avoid accidentally cutting out the appositional layer. Alternatively, surgical skin staples can be used (***Figure***).



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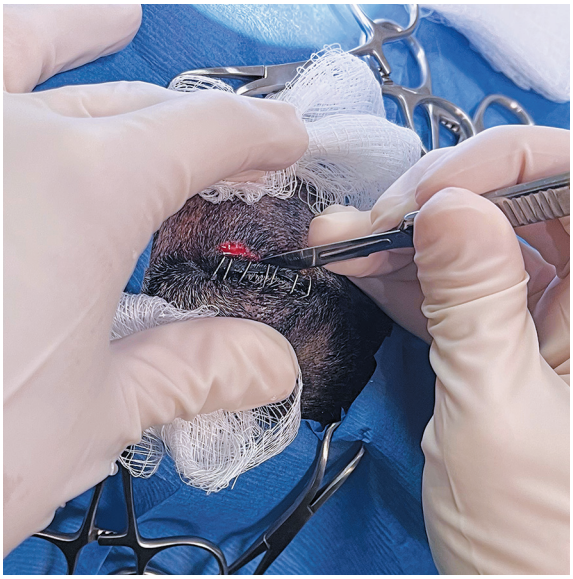
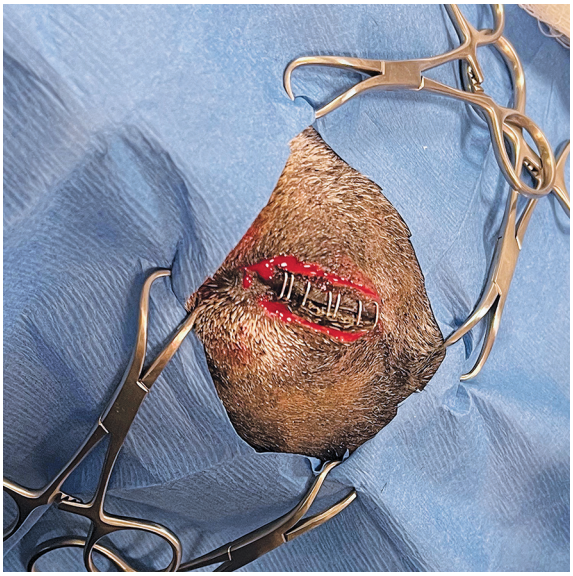
STEP 4

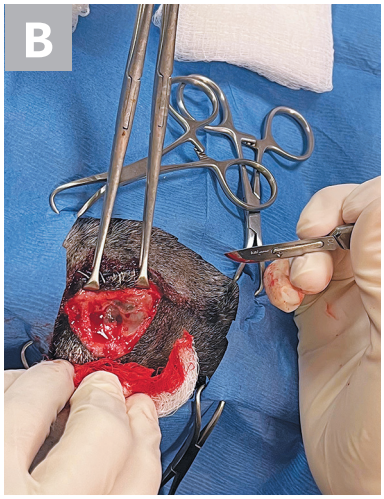
Using a #10 scalpel blade, make 2 elliptical skin incisions into the eyelids ≈2 mm from the lid margin, completely encircling and including the medial and lateral canthus.

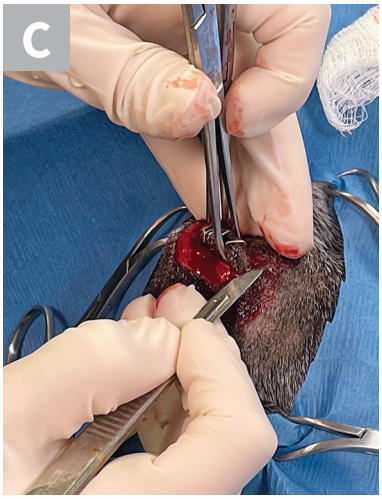




STEP 5

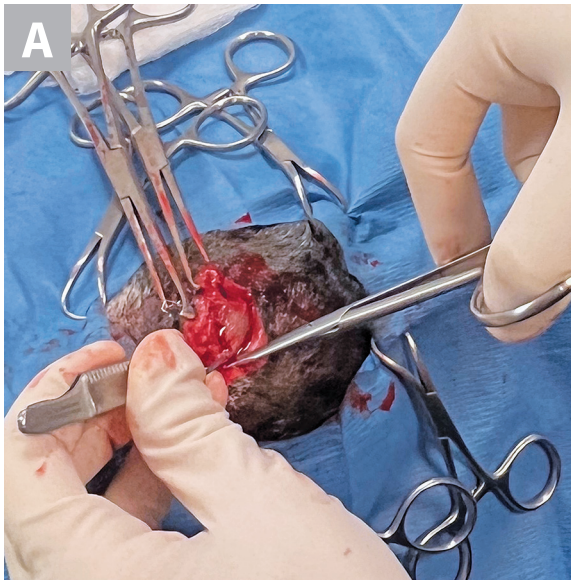
Use Allis tissue forceps to grasp the eyelid margins (only grasp tissue intended to be excised), creating mild traction to aid with initial dissection (***A***). Transect the canthal ligaments, and dissect the superficial eyelid fascia with light sweeps of the scalpel blade until just posterior to the limbus (***B***, ***C***).

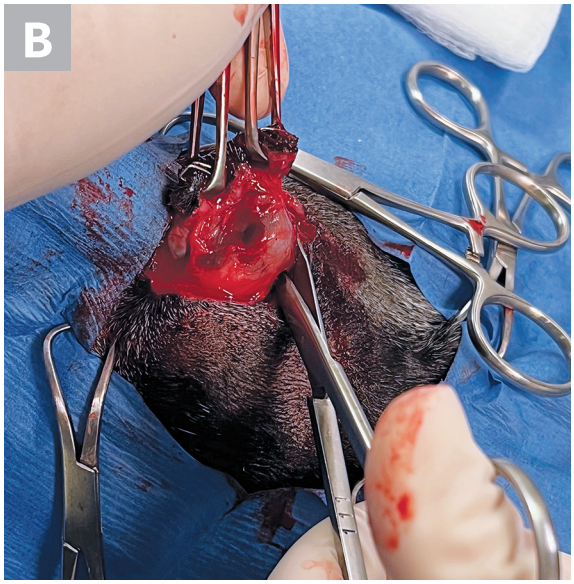




STEP 6

Perform deep dissection through the periorbital tissue with Stevens tenotomy scissors (***A***). Dissect toward the globe until the sclera is visualized, then extend the pocket around the globe with a combination of blunt dissection and cutting (***B***). Transect the extraocular muscles close to their scleral insertion, allowing the globe to be mobilized. Use caution in the dorsomedial location near the orbital rim to avoid transecting the medial angularis oculi vein. If this is transected, ligate the vessel.



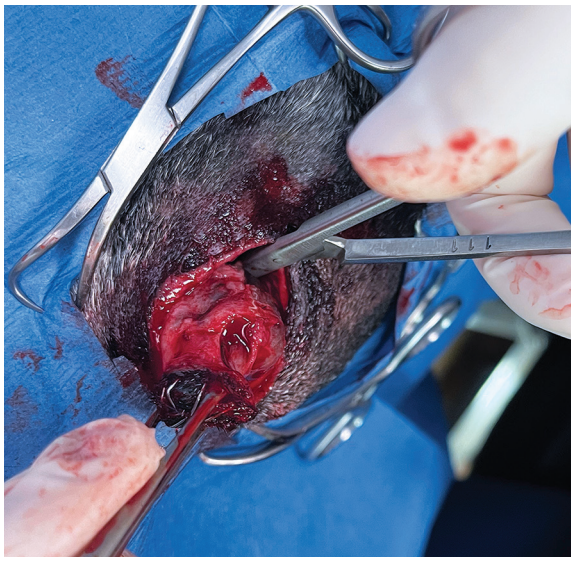


STEP 7

Place slight traction, reach behind the globe with the scissors held open, and cut the optic nerve.

Author Insight

The optic nerve should not be clamped before cutting to avoid damage to contralateral optic nerve fibers at the optic chiasm. Minimal traction to the ocular tissues is needed to protect the contralateral eye. Excessive traction on the eye should be avoided to limit the risk for oculocardiac reflex.



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STEP 8

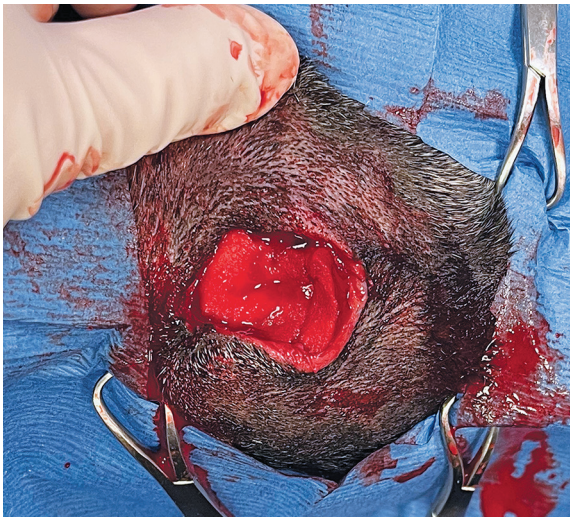
Remove the globe, pack the orbit with gauze sponges, and apply firm digital pressure for 2 to 3 minutes to control hemorrhage. Once hemorrhage is controlled, remove the gauze and irrigate the orbit with sterile saline.

STEP 9

Soak a sterile absorbable gelatin sponge with bupivacaine (optional) and place in the orbit.

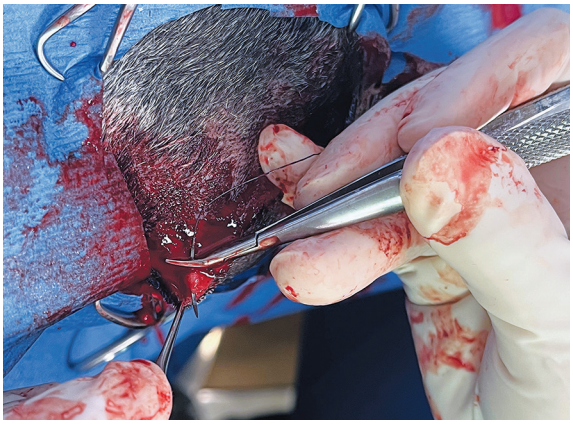
Author Insight

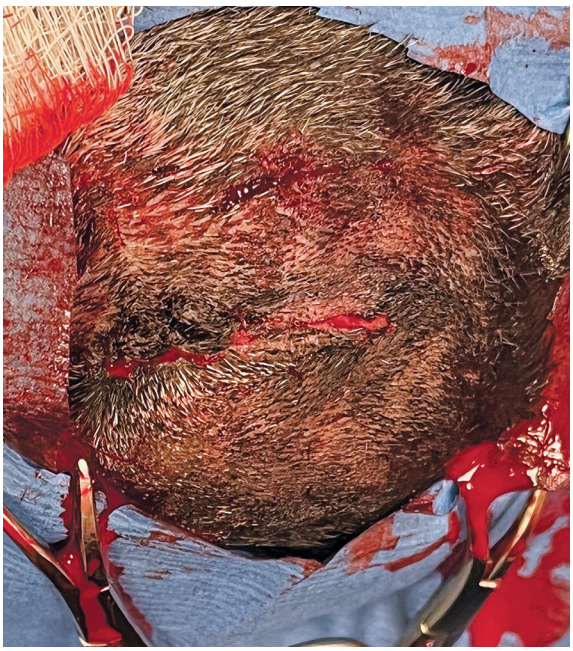
Absorbable gelatin sponges are typically absorbed in 4 to 6 weeks.



STEP 10

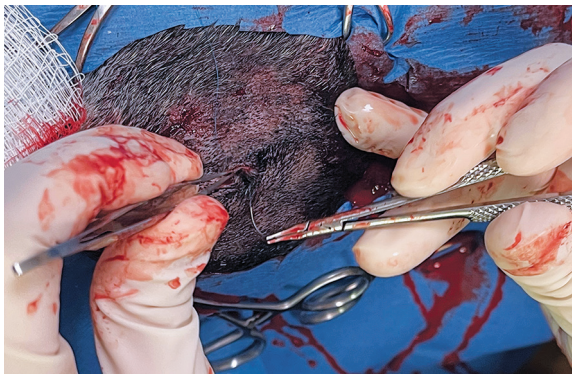
Close the deep fascial layers and subcutaneous tissues with 4-0 absorbable suture material in a simple continuous pattern.

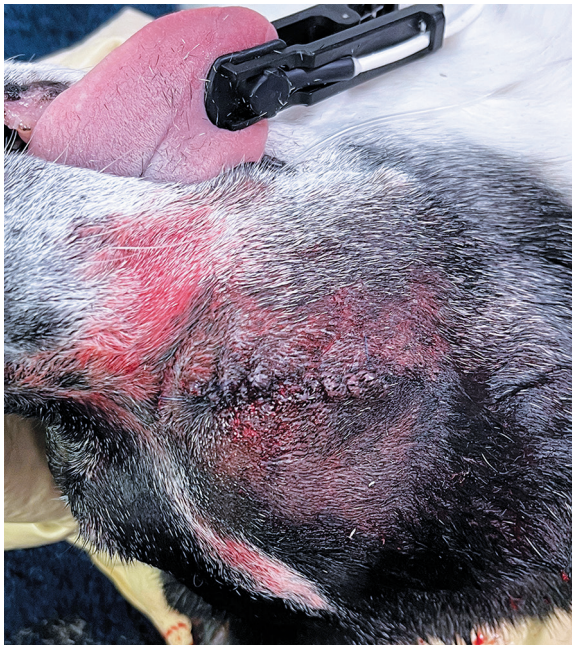




STEP 11

Close the skin with simple continuous or interrupted sutures using 6-0 nonabsorbable monofilament suture.





POSTOPERATIVE CARE

- Systemic antibiotics and systemic pain management should be given for 2 weeks postoperatively. Postoperative antibiotics should be administered if there is a break in sterility or noticeable abscessation in the orbit. Typically, cephalexin (22 mg/kg PO every 12 hours for 2 weeks) can be administered.
  - –Systemic NSAIDs should be used if not contraindicated to reduce surgical site inflammation.
  - –A cold compress can be applied for 10 to 15 minutes immediately following surgery to help reduce inflammation.
- Skin sutures should be removed after 10 to 14 days.
- Patients should wear an Elizabethan collar until sutures are removed to prevent self-trauma.
- Normal postoperative findings include mild serosanguinous drainage from the incision site and/or ipsilateral nostril for 2 to 3 days, as well as swelling and bruising of the incision site.
- Complications may include the following:
  - –Hemorrhage within the first few hours following surgery (most common) that can be controlled with cold compresses, pressure bandages, exercise restriction, and/or mild sedation
  - –Draining orbital fistulas due to incomplete removal of the medial canthus, conjunctiva, or third eyelid gland
  - –Orbital infection
  - –Orbital emphysema (less common; can occur in brachycephalic breeds)

Lyme Nephritis Review

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Exposure to *Borrelia burgdorferi* (Bb) is common, but less than 5% of exposed dogs show classic clinical signs.[1] As a result of climate change, increasing travel, increased proximity to deer and wildlife, and bird migration, tick exposure to both humans and pets has increased. The *Ixodes* tick is responsible for transmission of Bb along with other tick-borne diseases.[1,2] Despite precautions, preventatives, and vaccines, some dogs develop clinical illness from Bb. The most common manifestation of illness is polyarthropathy. In most instances, Bb exposure is found incidentally on annual serologic screening tests. In other instances, serologic screening may be specifically ordered due to clinical signs of illness. This article will briefly review the more complicated case of Lyme nephritis and treatment in dogs.

Borrelia burgdorferi is a tick-borne spirochete organism first identified in 1975 in Lyme, CT. In humans, the clinical signs can be severe, including flu-like symptoms, fever, skin rashes, and chronic illness, such as arthritis, and cardiac and neurologic symptoms. In contrast, the majority of dogs with exposure to *Borrelia burgdorferi* (Bb) have no clinical signs. If present, clinical signs can include lameness, fever, and anorexia. Often, these signs will be self-limiting or, if treated rapidly, responsive to antibiotic therapy.[2, 3, 4] Cases of neurologic, ocular, and cardiac complications of lyme disease are not well documented in dogs.[3, 5, 6]

Lyme nephritis

Lyme nephritis (LN) is rare and only occurs in approximately <1-2% of Lyme positive cases, with Labradors and Golden Retrievers being overrepresented.[1, 2, 4] Experimental models of Lyme disease failed to show renal disease or proteinuria, making study of this disease difficult.[1, 2] No experimental model for Lyme nephritis exists.[1, 2, 4]

The presentation of LN can vary widely with the duration of clinical signs ranging from 2 weeks to 6-8 weeks, on average.[1, 4] Signs can include vomiting, lethargy, and anorexia or, more severely, fever, weight loss, ascites, effusions, or edema.[1] Protein-losing nephropathy (PLN) of any type includes proteinuria, hypoalbuminemia, and when afvanced often azotemia, along with hypertension and hypercoagulability.[1,2,4] In the severe cases, signs can often progress quickly, and death can occur due to secondary complications within weeks. Serologic evidence of Bb exposure and proteinuria alone is not pathognomonic for Lyme nephritis and other causes of proteinuria must be excluded. Elevations of the urine protein creatinine ratio (UPC) can be secondary to urinary tract infections, amyloidosis, immune mediated disease, neoplasia, genetic disease, or toxins.[1] Renal biopsy, if done early in the disease, can aid in diagnosis and allow early intervention and treatment.

Unlike leptospirosis, the renal changes associated with Lyme nephritis are not due to the organism itself but rather an immune mediated process. Renal biopsies from moderate to severely affected dogs revealed immune mediated membranoprofliferative glomerulonephritis (MPGN), tubular necrosis/regeneration, and interstitial inflammation, along with subendothelial C3, IgG and IgM deposits.[1, 7, 11] These findings are different from those seen in other types of glomerulonephritis.[11] Immunohistochemical (IHC) staining of renal biopsies show some positive staining with antibodies directed against Bb antigen, but overall results were discordant with PCR for Bb and seemed to point toward immune complex disease rather than direct spirochete involvement.[14] Studies have shown LN to be a result of the immune complex disease and not directly related to the presence of the pathogen.[14, 13]

A study was done in 2008 to evaluate for the presence of the B burgdorferi organisms in the kidneys of serologically Lyme positive dogs.[9] Twenty-six affected dogs and 10

control dogs were evaluated, and there was minimal evidence of the presence of Bb or other bacterial organism in the renal tissue of the dogs suspected of Lyme nephritis.[8] Studies to detect *Borrelia burgdorferi* DNA in tissues in Lyme positive or Lyme suspect dogs was low at only 7% of the 38 dogs affected. The study concluded the DNA was rarely found in tissues from naturally infected dogs and there was no correlation between the IHC staining and results of the PCR assay in renal tissues.[13] The positive IHC staining can be consistent with antigen leading to immune complex disease, even when the pathogen is cleared.[14] Only rare renal tissues were positive for spirochete DNA, even when the dogs had strong clinical and pathologic evidence of LN. These finding lend support to the immune mediated process of glomerulonephritis in these dogs.[7, 13, 14]

The diagnosis of Lyme disease as mentioned, is not straightforward and is based on positive serology, a history of exposure to *Ixodes* spp., presence of the disease in the region, and compatible clinical signs and most importantly, exclusion of other causes.[1] There several patient side/POC tests for Bb such as the Idexx 4Dx Snap Test which also test for other tick borne diseases. A C6 (Idexx) antibody test is a quantitative test for Lyme disease which can detect antibodies at 3-5 weeks after infection and can remain positive for over 6 months. The level of antibody detected, however, does not correlate to severity of disease. The updated Lyme Consensus statement reports that 4/6 panelist suggest to check for a decrease in C6 levels after treatment, but there is no agreement that it should be used to guide treatment or evaluate responses.[2] Per the laboratory's instructions, if treated dogs are retested 6 months after infection, the C6 level should be <50% of pretreatment levels.[1, 2, 4] Cornell University's Multiplex Assay measures different outer surface proteins, A, C, and F. These outer surface proteins

help differentiate vaccination, as well as early or chronic infection. Antibodies to OspA serve as markers for vaccination, as OspA is generally only expressed by Bb within the tick and not expressed on Bb transferred to the dog. OspA is a component of all Bb vaccines, while OspC and OspF serve as markers of infections. OspC is present approximately 2-3 weeks after infection and levels start to decline after 2-3 months. They are then undetectable by 4-5 months post-infection. The OspF outer surface protein is an indicator of chronic infection and is detectable by weeks 5-8 post-infection. OspF and C6 antibody have a close correlation.[7]

Treatment

There is no consensus on the best treatment for Lyme nephritis.[1,2,3] If a dog presents asymptomatic and Bb serology positive, a urinalysis should always be performed to evaluate for proteinuria. If the urine is culture negative yet proteinuric, then antibiotic therapy and appropriate therapy as needed for proteinuria or PLN should be initiated.[1, 2, 3, 4] Doxycycline is the most frequent choice at 10mg/kg PO q24h for 30 days. Other potential therapies include amoxicillin 20mg/kg PO q8h for 30 days and cefovecin (Convenia) 8mg/kg SC q14d for two doses.[5] Doxycycline is the preferred antibiotic because it covers other diseases also spread by Ixodes spp ticks such as anaplasmosis. Obviously other causes for PLN should be tested specific to the geographic area and the clinical signs. Leptospirosis can often mimic signs of PLN and serology testing should be submitted. Early cases of Leptospirosis can have negative titers and convalescent titers should be checked in 2-4 weeks. A full vector-borne disease panel is recommended to screen for other infectious agents (*Ehrlichia, Babesia, Bartonella, Anaplasma,* and others pending geographic location) as Bb seropositivity indicates prior tick exposure.

A cortical renal biopsy, although needed for confirmation of active immune complex disease, is not always an option.[1, 2, 3] The risks associated with the procedure must be considered, which include bleeding, worsening azotemia, and thrombus. If the disease progresses, or there is worsening azotemia and hypoalbuminemia, then therapy for PLN along with immunosuppression therapy is recommended.[2, 3] If the patient is still eating and drinking, oral medications can be prescribed, including appropriate antibiotics, antithrombotics, antihypertensives, ACE inhibitors, or angiotensin receptor blockers, along with renal diets and phosphate binders. Subcutaneous fluids can be used judiciously in some cases with monitoring for fluid overload and edema. If azotemia with anorexia, nausea, and vomiting, and worsening clinical signs continues, supportive care and hospitalization is needed. Due to the associated hypoalbuminemia, however, crystalloid fluid therapy may not be an option and will only result in further third spacing, edema, and fluid overload. Oncotic support can be provided with colloids or albumin transfusion and further supportive care provided with IV administration of antibiotics, antinausea medications, antacids, and gastroprotectants. Additionally, feeding tubes can be used to provide nutrition and enteral fluids for hydration.

Immunosuppressant therapy based on the GN study group guidelines includes mycophenolate (7.5-10 mg/kg PO every 12 hours) and a tapering course of prednisone (1 mg/kg bid for 4 days, with a 2 week taper) .[1, 2, 3] Other immunosuppressants can be used if mycophenolate is not tolerated but there is no consensus on which drug is preferred.[2] Gastrointestinal side effects are the most common adverse side effect of mycophenolate which can often be avoided with dose reduction.

Success in treatment can vary, with some dogs succumbing to disease early in its presentation. Other dogs will stabilize but with ongoing proteinuria and/or azotemia. Although a rare presentation of Lyme disease, a diagnosis of Lyme nephritis can be devastating news with a poor prognosis,[1] but there is some hope in present treatments and aggressive supportive care. It is important to try to diagnose early, as well as rule out other treatable diseases with a better prognosis. Prevention of Lyme disease with year-round tick control and vaccination is essential to minimize the risk of Lyme polyarthritis or Lyme nephritis.[9,15]

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Top 5 Uses for Gabapentin in Dogs & Cats

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Gabapentin is a widely used antiepileptic and analgesic designed to function as a centrally acting gamma-aminobutyric acid (GABA)-receptor agonist.[1] Although gabapentin is structurally related to the GABA molecule, it does not bind to or alter the GABA receptor and is believed to bind instead to the alpha2delta subunit of voltage-gated calcium channels on presynaptic neurons in the CNS, blocking influx of calcium into the nerve terminal and decreasing release of excitatory neurotransmitters.[2,3]

Gabapentin is FDA-approved in humans for use as an anticonvulsant, treatment of pain associated with postherpetic neuralgia and fibromyalgia, and treatment of neuropathic pain associated with diabetes and spinal cord injuries.[3] Gabapentin is the seventh most frequently prescribed drug in the United States; use has increased significantly in human medicine and is often (>80%) extra-label.[4,5]

A survey of clinicians found that gabapentin use in veterinary medicine is similar to use in human medicine; 69% of respondents indicated they prescribe gabapentin on a daily or weekly basis, most commonly for acute and chronic pain (extra-label).[1]

Following are the author's top 5 recommended uses for gabapentin based on mechanism of action and physiology of pain.

TOP 5 USES FOR GABAPENTIN IN DOGS & CATS

1. Preclinic Sedation
2. Neuropathic Pain
3. Breakthrough Pain
4. Osteoarthritis
5. Cancer Pain

GABA = gamma-aminobutyric acid

1 Preclinic Sedation

At-home administration of oral sedatives/anxiolytics before visiting the clinic can reduce patient anxiety and fearful behaviors by allowing drugs to take effect before the patient encounters stressors. Gabapentin is used extra-label as an antianxiety medication in humans[6-8]; administration in cats (50-100 mg/cat PO) can decrease stress scores.[9,10]

The Chill Protocol (ie, combination drug protocol that includes gabapentin, melatonin, and oral transmucosal acepromazine) is an option for preclinic sedation developed at the Cummings School of Veterinary Medicine at Tufts University to manage fearful and aggressive dogs and cats.[11] Dose-dependent sedation is a common adverse effect of gabapentin administration in veterinary patients[12,13]; high doses of gabapentin (ie, 20-25 mg/kg PO the evening before the appointment and 20-25 mg/kg PO at least 1-2 hours before the appointment) are incorporated in the Chill Protocol to induce preclinic sedation.[11]

GABAPENTIN DOSAGE INFORMATION

- Use in veterinary patients is extra-label.
- Conditions associated with neuropathic pain
  - –Dogs: 10 mg/kg PO every 8 hours[17]
  - –Cats: 8 mg/kg PO every 6 hours[18]
  - –Frequent administration maintains minimum target plasma concentrations in dogs and cats because gabapentin is rapidly absorbed and eliminated.[17]
- Preclinic sedation
  - –Dogs/cats: 20 to 25 mg/kg PO the evening before the appointment and 20 to 25 mg/kg PO at least 1 to 2 hours before the appointment[11]
  - –Sedation is likely in both dogs and cats at 20 mg/kg PO.
- The human oral liquid product contains xylitol, which is toxic to dogs.

2 Neuropathic Pain

Neuropathic pain (eg, intervertebral disk herniation, plexus avulsions, nerve root impingement) is caused or initiated by a primary lesion in the CNS or peripheral nervous system, including damage or injury to nerves that transfer information from the skin, muscles, and/or other parts of the body to the brain and spinal cord.[14,15] Imbalances between excitatory and inhibitory pain signaling, as well as modulation of pain messages in the CNS, contribute to development of neuropathic pain.[15]

Gabapentin inhibits presynaptic calcium channels, thus decreasing release of excitatory neurotransmitters (eg, substance P, glutamate, glycine) that amplify pain signals by binding to postsynaptic neurokinin-1 (ie, NK-1), *N*-methyl-D-aspartate (ie, NMDA), and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (ie, AMPA) receptors.

Neuropathic pain is a complex pain state, and several drug classes are often required to reduce inciting nociceptive afferent impulses.[14] Gabapentin can be included in a multimodal treatment plan in conjunction with other analgesic drugs (eg, NSAIDs, opioids, *N*-methyl-D-aspartate–receptor antagonists).[14]

3 Breakthrough Pain

Pain transmission involves conversion of a noxious stimulus to an electrical signal transmitted by peripheral sensory fibers to the dorsal horn of the spinal cord.[14] Pain signals are either amplified or suppressed by endogenous neurotransmitters or analgesic drugs in the dorsal horn and progress to the brain, where the signal is consciously perceived. Untreated amplification of pain signals in the dorsal horn can lead to maladaptive or chronic pain states.[14]

Gabapentin can be added to an analgesic regimen to manage heightened pain states if first-line analgesics are insufficient. Inhibition of presynaptic calcium channels can help reduce excitatory pain signaling, thus improving analgesia. Gabapentin

may also act synergistically in combination with other analgesics, reducing required doses and minimizing adverse effects (eg, dysphoria, sedation). Heightened pain states that may require adjunct analgesics (eg, gabapentin) include polytrauma, pathologic fractures, thrombosis, and extensive inflammation (eg, peritonitis, fasciitis).[14]

4 Osteoarthritis

Osteoarthritis is a chronic inflammatory condition involving joint pain that results in decreased mobility and muscle weakness[14]; however, there may also be a neuropathic component.[16] Inflammation of the affected joint activates peripheral nociceptors innervating the synovial capsule, periarticular ligaments, periosteum, and subchondral bone. Repetitive activation results in peripheral sensitization and abnormally excitable pain pathways in the peripheral nervous system and CNS.[16]

Osteoarthritis treatment can be complex, and recommendations include baseline analgesics (eg, NSAIDs) and nonpharmacologic treatments (eg, exercise, weight management).[14] Gabapentin is an adjunct analgesic that can be incorporated if first-line treatments are insufficient.

5 Cancer Pain

Cancer pain can range in severity, depending on the location and type of cancer. Patients may experience inflammatory pain due to tumor necrosis or pain caused by direct pressure of the tumor on nerves or muscles. Metastatic involvement of bone is also a frequent cause of cancer pain and can be associated with clinical signs related to neuropathic pain.[14]

A multimodal approach using several classes of drugs is most effective. Therapies that decrease tumor activity, reduce inflammation, or target neuropathic pain can help treat cancer pain. First-line agents often include NSAIDs with the addition of opioids and adjunctive drugs (eg, gabapentin) as indicated.[14]

DRUG OF ABUSE

Human recreational drug users may ingest supraclinical amounts of gabapentin for intoxication or use gabapentin to augment the effects of illicit opioids.[3-5,19-23] Patients who overdose and are taken to an emergency room are more likely to die or require a ventilator if an illicit opioid was combined with gabapentin.[4,5,22] Deaths due to overdose in which gabapentin was also detected doubled between 2019 and 2020.[4]

INAPPROPRIATE USES FOR GABAPENTIN

- Single agent for acute postoperative pain
  - –Inflammation is the most common component of acute postoperative pain. Gabapentin modulates pain signals from the periphery but does not treat inflammation and can reduce (but will not stop) pain signaling in the CNS.
- Renal compromise
  - –Gabapentin is removed from the body via the kidneys and should be used with caution in patients with renal insufficiency, as increased adverse effects (eg, sedation, hypotension) are possible.[24-26]
- As-needed administration
  - –Frequent administration of gabapentin is required to maintain adequate plasma concentrations in dogs and cats.[17,18] Administration on an as-needed basis or at intervals less frequent than indicated by pharmacokinetic studies can result in insufficient plasma concentrations and lack of efficacy.
- Long-term postoperative sedation
  - –Sedation is a common adverse effect of gabapentin, particularly with administration of high doses[12,13]; however, this effect diminishes over time, and gabapentin is unlikely to provide sedation over several days or weeks.
- Pelvic-end weakness
  - –Ataxia is a common adverse effect of gabapentin.[12] Administration in patients with pelvic-end weakness may exacerbate signs and decrease the ability to ambulate without assistance.

Continues ▶

Conclusion

Gabapentin has a narrow indication for use in veterinary patients, but administration is common. Caution should be used when prescribing gabapentin, particularly for use as a sole analgesic for conditions with little evidence for efficacy (eg, acute postoperative pain).[1]

Gabapentin can be abused in humans, and prescriptions for veterinary patients can be diverted for human recreational use (see ***Drug of Abuse***, previous page). Gabapentin should thus not be prescribed when it is unlikely to be effective (see ***Inappropriate Uses for Gabapentin***, previous page), the quantity should be limited, and restrictions should be placed on refill authorizations.

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ABNORMAL RESPIRATORY SOUNDS

Leah A. Cohn, DVM, PhD, DACVIM (SAIM)
University of Missouri

THORACIC AUSCULTATION*

Decreased bronchovesicular sounds

Adventitial sounds

Increased bronchovesicular sounds

DIAGNOSIS
Rule out:
- Shallow inspiration
- Obesity
- Atelectasis
- Pleural effusion
- Pneumothorax
- Thoracic mass

Wheezy/ronchus (ie, continuous "musical" sounds)

Crackles/rales (ie, discontinuous "Velcro"-like sounds)

Pleural friction rub (ie, cyclic "grating" sounds)

DIAGNOSIS
Rule out:
- Pulmonary edema
- Pneumonia
- Increased turbulence of airflow
- Hyperpnea
- Referred upper airway noise

DIAGNOSIS
Rule out:
- Airway obstruction
- Airway secretions
- Asthma
- Severe bronchitis

INVESTIGATION
Radiographic imaging
Alveolar pattern‡

DIAGNOSIS
Rule out:
- Pleuritis

YES

NO

Cranioventral distribution

Perihilar distribution

Caudodorsal/diffuse

DIAGNOSIS
Rule out:
- Bacterial pneumonia
- Aspiration pneumonia
- Hemorrhage

DIAGNOSIS
Rule out:
- Congestive heart failure

DIAGNOSIS
Rule out:
- Non cardiogenic pulmonary edema (eg, electrocution, postseizure)
- Acquired respiratory distress syndrome
- Fungal pneumonia
- Protozoal pneumonia
- Rickettsial pneumonitis
- Hemorrhage

DIAGNOSIS
Rule out:
- Pulmonary fibrosis
- Early pulmonary edema
- Early aspiration pneumonia

*Abnormal sounds on auscultation can occur alone or in combination; they may also be heard throughout the thorax or only in some areas.

TIPS & TACTICS

- Several abnormal respiratory sounds are heard without a stethoscope (eg, stertor, stridor), but others are heard only on thoracic auscultation. Thoracic auscultation requires intense attention to detail. Auscultation should be done in a quiet environment.
- Growling, purring, and panting make accurate auscultation impossible.
- Deep breaths facilitate auscultation; holding the nostrils closed for a few moments will encourage 1 or 2 deep breaths afterward.
- Normal lung sounds are described as bronchovesicular, but bronchovesicular sounds can indicate disease when they are increased or decreased in intensity or heard in an abnormal location. Adventitial sounds are always abnormal.
- Adventitial sounds or altered bronchovesicular sounds can occur alone or in combination.
- Crackles are usually best heard on inspiration; inducing a cough may facilitate auscultation when the cough subsides.

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2022 Veterinary Therapeutics: Updates, Highlights, & Practical Considerations

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Plumb's

Several novel veterinary drug products have been approved by the FDA. This article highlights some of the new drugs marketed for use in small animals and summarizes pharmacology, dosages, adverse effects, and other key information required for safe use. Also included are drugs previously approved by the FDA that have been granted additional indications, as well as first generic approvals for topical formulations.

New Approvals

Medetomidine/Vatinoxan

Approved Use

The medetomidine/vatinoxan combination product is a sedative–analgesic injection FDA-approved for use in dogs to help facilitate examinations, clinical procedures, and minor surgical procedures.

Pharmacology

Vatinoxan, a peripherally acting alpha-2–adrenergic antagonist, attenuates the adverse cardiovascular effects (eg, bradycardia) of medetomidine, an alpha-2–adrenergic agonist. Vatinoxan can alter the pharmacokinetics of medetomidine (as well as other sedatives and anesthetics [eg, midazolam, alfaxalone]),[1,2] resulting in a typically shorter duration of sedation of the combination product (ie, medetomidine/vatinoxan) than an equivalent dose of medetomidine alone. Medetomidine/vatinoxan should thus not be administered interchangeably with single-agent medetomidine in sedative and anesthetic protocols.

Contraindications

This combination drug is contraindicated in dogs hypersensitive to medetomidine or vatinoxan; dogs

with cardiac disease, respiratory disorders, shock, or severe debilitation; dogs that have or are at risk for developing hypoglycemia; and dogs stressed due to heat, cold, or fatigue. Medetomidine/vatinoxan should not be administered to dogs with pre-existing hypotension, hypoxia (hypoxemia), or bradycardia and should be used with caution in dogs with hepatic or renal disease, as safe use with these conditions has not been evaluated.[3] This drug should not be administered to cats, as significant hypotension has been noted.[4-6]

Adverse Effects

Medetomidine/vatinoxan is well tolerated in dogs. In clinical trials, decreased body temperature (≤99°F [37°C]) was observed in ≈50% of treated dogs, but clinical hypothermia was rare.[3]

Dosage

Medetomidine/vatinoxan dosage should be calculated based on medetomidine 1 mg/m^2 IM; the product label contains a weight-based dosage table.[3]

Additional Information

Atipamezole (5,000 µg/m^2 IM) can reverse the central and cardiovascular effects of the combination product (ie, medetomidine's effects); sedation reversal occurs 5 to 10 minutes after atipamezole administration.[7]

Crofelemer

Approved Use

Crofelemer is conditionally FDA-approved (pending full demonstration of effectiveness) for treatment of chemotherapy-induced diarrhea in dogs. Other causes of diarrhea (eg, infection, toxicosis) should be ruled out prior to crofelemer use.

Pharmacology

Crofelemer inhibits 2 types of chloride channels at the luminal membrane of intestinal epithelial cells, blocking chloride ion secretion and accompanying high-volume water loss that occurs with diarrhea. At approved dosages, crofelemer is not absorbed from the GI tract.

Contraindications

Crofelemer is contraindicated in patients hypersensitive to it. Administration in combination with other antidiarrheal agents (eg, hyoscyamine, loperamide) has not been studied and warrants caution.

Adverse Effects

At approved dosages, adverse effects are uncommon.

Dosage

Dogs ≤140 lb (63.6 kg) can be administered 125 mg/dog PO every 12 hours for 3 days. Dogs >140 lb (63.6 kg) can be administered 250 mg/dog PO every 12 hours for 3 days.[8] This drug can be administered with food or on an empty stomach and should be given as intact tablets (ie, not split, broken, or crushed); one additional dose can be administered if the tablets are chewed. Extra-label use of conditionally approved drugs is not permitted by the FDA.

Frunevetmab

Approved Use

Frunevetmab is the first safe and effective FDA-approved drug to control pain associated with osteoarthritis in cats.

Pharmacology

Frunevetmab is a cat-specific immunoglobulin G monoclonal antibody that binds to nerve growth factor (NGF), decreasing NGF-induced peripheral sensitization, neurogenic inflammation, and increased perception of pain.[9]

Frunevetmab is the first safe and effective FDA-approved drug to control pain associated with osteoarthritis in cats.

NGF = nerve growth factor

Continues ▶

Contraindications

Fetal abnormalities, increased stillbirths, and increased postpartum fetal mortality have been noted in rodents and primates receiving anti-NGF monoclonal antibodies, and frunevetmab is contraindicated in breeding cats and in pregnant or lactating queens.[10] Frunevetmab is also contraindicated in cats hypersensitive to it. This is a feline-specific product that should not be used in any other species.[10]

Adverse Effects

Adverse effects include injection site pain (≈11%), injection site reactions (≈5%; eg, scabbing, dermatitis, alopecia, pruritus, swelling), and GI signs (≈7%-13%; eg, vomiting, diarrhea, anorexia). Worsening of existing renal insufficiency (6.6%), dehydration (4.4%), weight loss (3.3%), and gingival disorders (2.2%) have also been reported. Cats can form antifrunevetmab antibodies that may result in loss of effectiveness.[10]

Dosage

Target dosage range is 1 to 2.8 mg/kg SC per month.

Additional Information

Frunevetmab has not been studied in combination with other medications, including NSAIDs. In humans given a humanized anti-NGF concurrently with long-term NSAIDs, incidence of rapidly progressing osteoarthritis was increased.[11,12] The significance of this finding for veterinary patients is uncertain; rapidly progressing osteoarthritis has not been reported in cats.

Analgesic effect is ≈2 to 3 weeks after administration.[7,13,14] Pet owners considered treatment to be successful in ≈75% of arthritic cats given frunevetmab in the target dosage range.[13] The long-term safety and efficacy of this drug are unknown.

NGF = nerve growth factor

Buprenorphine Transdermal Solution (C-III)

Approved Use

Buprenorphine transdermal solution is FDA-approved for one-time administration to control postoperative pain in cats, providing an additional option for short-term analgesia.

Pharmacology

This drug is formulated for rapid absorption and sequestration into the stratum corneum of cats, resulting in continuous systemic buprenorphine delivery.

Contraindications

Buprenorphine transdermal solution has not been evaluated in cats with renal, hepatic, cardiac, or respiratory disease and should be used with caution in these patients. Because this opioid formulation delivers the drug into the systemic circulation, this drug should be used cautiously in patients with head trauma, increased CSF pressure, or other CNS dysfunction (eg, coma), as any degree of respiratory depression could result in excessive partial pressure of arterial carbon dioxide with a subsequent increase in intracranial pressure.

Adverse Effects

Hyperthermia and sedation appear to be the most common adverse effects.

Dosage

Tube size (0.4 mL or 1 mL) should be based on patient body weight and the target dose (2.7-6.7 mg/kg) administered via topical application of the entire tube contents directly on healthy skin at the dorsal cervical area of the base of the skull 1 to 2 hours preoperatively. Analgesia occurs within 1 to 2 hours of application and lasts up to 4 days.[15]

Additional Information

This product is a highly concentrated buprenorphine solution and should not be dispensed for at-home administration. Clinicians and veterinary staff should be trained in safe handling and proper administration techniques to minimize the risk

for accidental exposure, which could result in life-threatening respiratory depression. Impermeable gloves, protective glasses, and a laboratory coat should be worn when applying the solution. Following administration, a drying time of ≥30 minutes should be allowed before contact is made with the application site.

Buprenorphine is a Schedule III (C-III) controlled substance, and it is important to follow local, state, and federal requirements for storage, record keeping, disposal, and reporting. The package insert contains a warning related to potential human abuse of opioids and the risk for drug diversion and/or abuse that should be considered when storing, administering, and disposing of buprenorphine transdermal solution.[15]

Updated Indications

Fluralaner

Fluralaner is now indicated for 2-month treatment and control of *Haemaphysalis longicornis* (ie, Asian longhorned tick) infestations in cats and kittens.[16]

Pimobendan

Pimobendan is conditionally FDA-approved (pending full demonstration of effectiveness) for use in delaying the onset of congestive heart failure in dogs with stage B2 preclinical myxomatous mitral valve disease.[17]

Sarolaner/Moxidectin/Pyrantel

The combination sarolaner/moxidectin/pyrantel chewable tablet is FDA-approved for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks and for the treatment and control of fourth-stage larvae and immature adult hookworm (*Ancylostoma caninum*).[18]

First Generic Approvals

The first generic approvals were given for imidacloprid and moxidectin topical solution and florfenicol, terbinafine, and mometasone otic solution.

ADVERSE DRUG EFFECTS

The FDA continues to monitor drug safety after approval is granted. Suspected adverse effects should be reported to the product's manufacturer or the FDA. To learn more, scan the QR code or see ***Suggested Reading***, next page.

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Suggested Reading

FDA Center for Veterinary Medicine. How to report animal drug and device side effects and product problems. FDA website. Updated June 15, 2022. Accessed November 22, 2022. https://www.fda.gov/animal-veterinary/report-problem/how-report-animal-drug-and-device-side-effects-and-product-problems#report

2-MINUTE TAKEAWAYS

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.

Slurry Preparation: A Novel Cytology Technique for Skin Lesions in Dogs

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In the literature

Rich N, Brune J, Duclos D. A novel cytological technique for bacterial detection on canine skin. *Vet Dermatol*. 2022;33(2):108-e30. doi:10.1111/vde.13036

THE RESEARCH ...

Impression smear and tape-strip preparations are traditional and validated skin cytology methods for diagnosis and monitoring of suspected bacterial or *Malassezia* spp overgrowth.

This study compared slurry preparation, a novel cytologic sampling method, with traditional methods to detect bacteria and *Malassezia* spp in 30 dogs presented with atopic dermatitis that had lesions consistent with superficial bacterial pyoderma and/or *Malassezia* spp dermatitis. Samples were collected using impression smear, tape-strip, and slurry preparation methods and stained with modified Wright-Giemsa stains.

For slurry preparation, a microspatula with a flat-ended blade was used to scrape the surface of a lesion; debris (including scale and crust) was collected on a glass slide. One drop of sterile water was placed on the slide and gently mixed via rocking. The slide was then briefly heated on a hot plate, after which the slurry was mixed and larger debris macerated with a wooden applicator stick, yielding an opaque liquid. Larger, unmacerated debris was removed from the sample, and the preparation was again briefly heated to dry remaining water. This preparation method took 2 to 3 minutes.

Slurry preparation identified significantly higher numbers of bacteria compared with other techniques; however, tape-strip cytology detected more yeast than slurry preparation.

Slurry preparation is a reasonable alternative to impression smears and tape-strip preparation for crusted and scaly lesions to improve chances of identifying bacterial infection. The authors recommend sampling pustules with impression smears instead of the slurry method, as pustules need to be ruptured prior to sampling.

… THE TAKEAWAYS

Key pearls to put into practice:

1 Skin cytology is recommended at both initial and follow-up examinations in patients presented for itching, scaling, crusts, or skin debris.[1,2] A combination of sampling methods can be used, depending on lesion appearance. For example, tape-strip cytology may be used on inflamed and scaly feet, impression smears may be used for a pustule on the ventral abdomen, and slurry preparation may be used for crusting on the dorsum during a single examination of a dog.

2 It may be easier for less experienced examiners to review impression smears and slurry preparations for bacteria, *Malassezia* spp, and inflammatory cells; tape-strip cytology preparations can appear more crowded to the untrained eye.[3]

3 Skin cytology allows for judicious oral antimicrobial use, as patients may have scaling or crust caused by *Malassezia* spp infection alone.[3] Routine use of skin cytology at follow-up examinations can also help guide timing of bacterial culture and enable correlation between culture results and morphologic characteristics of bacteria on cytology.[1]

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For use as a peripheral nerve block in cats only
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DOG Indication:
For single-dose infiltration into the surgical site to provide local postoperative analgesia for cranial cruciate ligament surgery in dogs.

CAT Indication:
For use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

DOG Dosage and Administration:
NOCITA is for single dose administration only. A dose of 5.3 mg/kg (0.4 mL/kg) is administered by infiltration injection into the tissue layers at the time of incisional closure for dogs. A single dose administered during surgical closure may provide up to 72 hours of pain control.

CAT Dosage and Administration:
NOCITA is for administration only once prior to surgery. Administer 5.3 mg/kg per forelimb (0.4 mL/kg per forelimb, for a total dose of 10.6 mg/kg/cat) as a 4-point nerve block prior to onychectomy. Administration prior to surgery may provide up to 72 hours of pain control.

Contraindications:
Do not administer by intravenous or intra-arterial injection. If accidental intravascular administration occurs, monitor for cardiovascular (dysrhythmias, hypotension, hypertension) and neurologic (tremors, ataxia, seizures) adverse reactions. Do not use for intra-articular injection. In humans, local anesthetics administered into a joint may cause chondrolysis.

Warnings:
Not for use in humans. Keep out of reach of children. NOCITA is an amide local anesthetic. In case of accidental injection or accidental topical exposure, contact a physician and seek medical attention immediately. Wear gloves when handling vials to prevent accidental topical exposure.

Precautions:
Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics. A safe interval from time of bupivacaine HCl, lidocaine or other amide local anesthetic administration to time of NOCITA administration has not been determined. The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.

The safe use of NOCITA in dogs or cats with cardiac disease has not been evaluated.

The safe use of NOCITA in dogs or cats with hepatic or renal impairment has not been evaluated. NOCITA is metabolized by the liver and excreted by the kidneys.

The ability of NOCITA to achieve effective anesthesia has not been studied. Therefore, NOCITA is not indicated for pre-incisional or pre-procedural loco-regional anesthetic techniques that require deep and complete sensory block in the area of administration.

The safe use of NOCITA in dogs for surgical procedures other than cranial cruciate ligament surgery has not been evaluated.

The safe use of NOCITA in cats for surgical procedures other than onychectomy has not been evaluated.

The safe use of NOCITA has not been evaluated in dogs or cats younger than 5 months old.

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

DOG Adverse Reactions:
Field safety was evaluated in 123 NOCITA treated dogs. The most common adverse reactions were discharge from incision (3.3%), incisional inflammation (2.4%), and vomiting (2.4%).

CAT Adverse Reactions:
Field safety was evaluated in 120 NOCITA treated cats. The most common adverse reactions were elevated body temperature (6.7%), surgical site infection (3.3%), and chewing/licking of the surgical site (2.5%).

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US Patent: 8,182,835; 8,834,921; 9,205,052

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For single-dose infiltration into the surgical site to provide local postoperative analgesia for cranial cruciate ligament surgery in dogs. For use as a peripheral nerve block to provide regional postoperative analgesia following onychectomy in cats.

Important Safety Information

NOCITA is for use in dogs and cats only. Do not administer concurrently with bupivacaine HCl, lidocaine or other amide local anesthetics. The safe use of NOCITA in dogs and cats with cardiac disease or with hepatic or renal impairment has not been evaluated. The safe use in dogs or cats younger than 5 months of age, that are pregnant, lactating, or intended for breeding has not been evaluated. The most common adverse reactions in dogs were discharge from incision, incisional inflammation and vomiting. The most common adverse reactions in cats were elevated body temperature and infection or chewing/licking at the surgical site. Please see accompanying brief summary for product safety information.

*In a field trial, Nocita reduced the need for post-op rescue pain treatment with opioids
**Cranial cruciate ligament

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See page 37 for product information summary.

Effect of Prazosin on Recurrent Urethral Obstruction in Cats

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In the literature

Conway DS, Rozanski EA, Wayne AS. Prazosin administration increases the rate of recurrent urethral obstruction in cats: 388 cases. *J Am Vet Med Assoc*. 2022;1-6. doi:10.2460/javma.21.10.0469

THE RESEARCH ...

Feline recurrent urethral obstruction (rUO) affects 11% to 58% of cats.[1] Prazosin, an alpha-1–adrenoceptor antagonist, is commonly used to prevent rUO despite lack of supporting veterinary clinical studies.[2,3] Prazosin has been recommended to reduce risk for recurrence because of its potential action as a urethral smooth muscle relaxant[2]; however, administration following urethral obstruction may cause increased patient stress from pill administration and adverse effects (eg, hypotension, lethargy, GI upset, ptyalism).

The objective of this study was to determine whether prazosin administration decreased the rate of feline rUO both prior to and within 14 days of discharge. Observational surveys were completed by clinicians who self-reported that they always or never prescribe prazosin. Development of rUO was compared in 302 (78%) cats administered and 86 (22%) cats not administered prazosin. There was no significant association between prazosin administration and risk for rUO prior to discharge; however, within 14 days following discharge, the cumulative rate of reobstruction was significantly higher in cats treated with prazosin (73 [24%]) compared with cats not treated with prazosin (11 [13%]).

Data from this study combined with data from selected prior prospective studies showed that cats given prazosin (24%) were more likely to develop rUO than cats not given prazosin (13%).[2,3] The only significant associations identified with risk for rUO were subjective difficulty performing catheterization and perception of a gritty urethra during catheterization.

The cause of prazosin's lack of efficacy is likely multifactorial. The distal 63% to 72% of the feline urethra is composed of striated muscle, which is not relaxed by alpha-1–adrenoceptor blockade.[4] Most urethral obstructions occur in the distal urethra where prazosin has no pharmacologic effect. Evidence that urethral spasms contribute to rUO in cats is lacking; treatment with urethral muscle relaxants may thus be ineffective.

The results of this study suggest that routine use of prazosin for prevention of rUO should be discouraged.

... THE TAKEAWAYS

Key pearls to put into practice:

1. Prazosin is ineffective at decreasing risk for rUO and may increase risk for recurrence.
2. Prazosin may increase patient stress, increase treatment costs, and cause adverse effects.
3. Study results suggest prazosin should not routinely be administered to prevent rUO in cats.

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Sternal Lymphadenopathy as a Prognostic Factor in Dogs with Splenic Malignancy

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In the literature

Kelsey J, Balfour R, Szabo D, Kass PH. Prognostic value of sternal lymphadenopathy on malignancy and survival in dogs undergoing splenectomy. *Vet Comp Oncol*. 2022;20(1):1-7. doi:10.1111/vco.12700

THE RESEARCH ...

Hemangiosarcoma is a malignancy that originates from vascular endothelial cells. The spleen is the most commonly affected primary organ in dogs, but additional sites have also been reported.[1] Other splenic sarcomas (eg, fibrosarcoma, leiomyosarcoma, extraskeletal osteosarcoma, undifferentiated sarcomas) are nonangiomatous, nonlymphoid tumors of connective tissue.

Several prognostic factors (eg, hemoabdomen, multiple splenic lesions, imaging findings, anemia, thrombocytopenia) have been evaluated in dogs with splenic hemangiosarcoma, with clinical stage of disease consistently correlated with overall survival time. Dogs with advanced clinical stage have poor outcomes compared with dogs with stage I disease.[2,3]

This retrospective study evaluated the clinical significance of sternal lymphadenopathy in 195 dogs undergoing splenectomy (most due to hemoabdomen), as well as prognostic significance in malignant splenic disease. Of these dogs, 102 (52.3%) were diagnosed with benign lesions, 74 (37.9%) were diagnosed with hemangiosarcoma, and 19 (10%) were diagnosed with malignancies other than hemangiosarcoma.

Incidence of sternal lymphadenopathy was 12.8% overall, 16.2% in the hemangiosarcoma group, 15.8% in the nonhemangiosarcoma malignancy group, and 9.8% in the benign process group.

Although sternal lymphadenopathy was not a predictor for malignancy in dogs with hemoperitoneum, dogs diagnosed with both hemangiosarcoma and sternal lymphadenopathy had shorter survival compared with dogs with hemangiosarcoma without sternal lymphadenopathy. Sternal lymphadenopathy may therefore have predictive value for survival of dogs with splenic malignancy.

… THE TAKEAWAYS

Key pearls to put into practice:

1. Sternal lymphadenopathy is not a predictor of malignancy in dogs with splenic masses, with or without hemoperitoneum.
2. Etiology of sternal lymphadenopathy is unknown. Microscopic evaluation is needed to rule out reactive versus metastatic disease processes.
3. Dogs diagnosed with both splenic hemangiosarcoma and sternal lymphadenopathy on thoracic radiographs had shorter survival compared with dogs without radiographic evidence of sternal lymphadenopathy.

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Suggested Reading

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Kahn SA, Mullin CM, de Lorimier L-P, et al. Doxorubicin and deracoxib adjuvant therapy for canine splenic hemangiosarcoma: a pilot study. *Can Vet J*. 2013;54(3):237-242.

Moore AS, Rassnick KM, Frimberger AE. Evaluation of clinical and histologic factors associated with survival time in dogs with stage II splenic hemangiosarcoma treated by splenectomy and adjuvant chemotherapy: 30 cases (2011-2014). *J Am Vet Med Assoc*. 2017;251(5):559-565.

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Optimal Propofol Infusion Rate in Dogs

Natalie Chow, DVM, DACVAA
MedVet Cincinnati
Fairfax, Ohio

MedVet Dayton
Moraine, Ohio

In the literature

Walters K, Lehnus K, Liu N-C, Bigby SE. Determining an optimum propofol infusion rate for induction of anaesthesia in healthy dogs: a randomized clinical trial. *Vet Anaesth Analg*. 2022;49(3):243-250. doi:10.1016/j.vaa.2021.07.006

Based on results of this study, the optimal rate of propofol infusion for induction of general anesthesia is 1 mg/kg/minute.

THE RESEARCH …

Propofol (premedicated dogs, 1-4 mg/kg; nonpremedicated dogs, 6.5 mg/kg; IV over 10-40 seconds and titrated to effect) is commonly administered for smooth, rapid induction of general anesthesia.[1] Benefits include rapid onset, short duration of action, quick redistribution, and short elimination half-life.[2] Adverse effects are dose dependent, with postinduction apnea and hypotension being most common.[3,4] Slow administration rate may decrease incidence of apnea.

This randomized, blinded clinical trial sought to determine the optimal propofol infusion rate for rapid tracheal intubation and reduction of postinduction apnea in healthy dogs. Dogs were randomly assigned into 5 groups. All dogs were premedicated with methadone (0.5 mg/kg IM) and dexmedetomidine (5 µg/kg IM). Thirty minutes after premedication, dogs were preoxygenated via facemask for 5 minutes. Each group was administered a different propofol infusion rate (0.5, 1, 2, 3, or 4 mg/kg/minute IV) for induction via syringe pump; infusions were discontinued once a dog was ready for intubation. After intubation, dogs were monitored until spontaneous breathing occurred. Time to intubation and duration of apnea were recorded. Cardiopulmonary variables (eg, heart and respiratory rates, oxygen saturation, blood pressure) were measured.

Propofol infusion rate had significant effects on both time to intubation and duration of apnea. Of the 60 dogs that completed the study, those that received propofol at 0.5 mg/kg/minute or 1 mg/kg/minute had a significantly shorter duration of apnea. None of the 60 dogs desaturated during the study. Between these 2 groups, intubation time was shorter in dogs that received propofol at 1 mg/kg/minute. Effect on blood pressure was not significantly different among groups.

Based on results of this study, the optimal rate of propofol infusion for induction of general anesthesia is 1 mg/kg/minute. Slow titration is recommended so propofol concentrations can equilibrate between the blood and the brain to achieve loss of consciousness with minimal adverse effects. Faster infusion rates lead to higher plasma concentration that exceeds the minimum dose to achieve unconsciousness, increasing the likelihood of apnea and hypotension.

This study only evaluated healthy dogs premedicated with methadone and dexmedetomidine. The cardiovascular effect of dexmedetomidine-induced vasoconstriction may have helped minimize the hypotensive effect of propofol. The effect of a priming bolus to help reduce total propofol induction dose was not evaluated.

… THE TAKEAWAYS

Key pearls to put into practice:

1. Propofol should be administered slowly IV and titrated to effect during induction; premedicated dogs require a lower dose.
2. Slow administration allows for a time delay between drug administration and loss of consciousness, as propofol concentrations need to equilibrate between the blood and brain.
3. Rapid administration can cause post-induction apnea, which can result in desaturation if patients are not preoxygenated prior to induction.

References

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3. Muir WW III, Gadawski JE. Respiratory depression and apnea induced by propofol in dogs. *Am J Vet Res*. 1998;59(2):157-161.
4. Cattai A, Rabozzi R, Ferasin H, Isola M, Franci P. Haemodynamic changes during propofol induction in dogs: new findings and approach of monitoring. *BMC Vet Res*. 2018;14(1):282. doi:10.1186/s12917-018-1608-8

VETORYL® CAPSULES
(trilostane)

5 mg, 10 mg, 30 mg, 60 mg and 120 mg strengths
Adrenocortical suppressant for oral use in dogs only.

BRIEF SUMMARY (For Full Prescribing Information, see package insert.)

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

DESCRIPTION: VETORYL Capsules are an orally active synthetic steroid analogue that blocks production of hormones produced in the adrenal cortex of dogs.

INDICATION: VETORYL Capsules are indicated for the treatment of pituitary and adrenal-dependent hyperadrenocorticism in dogs.

CONTRAINDICATIONS: The use of VETORYL Capsules is contraindicated in dogs that have demonstrated hypersensitivity to trilostane. Do not use VETORYLCapsules in animals with primary hepatic disease or renal insufficiency. Do not use in pregnant dogs. Studies conducted with trilostane in laboratory animals have shown teratogenic effects and early pregnancy loss.

WARNINGS: In case of overdosage, symptomatic treatment of hypoadrenocorticism with corticosteroids, mineralocorticoids and intravenous fluids may be required. Angiotensin converting enzyme (ACE) inhibitors should be used with caution with VETORYL Capsules, as both drugs have aldosterone-lowering effects which may be additive, impairing the patient's ability to maintain normal electrolytes, blood volume and renal perfusion. Potassium sparing diuretics (e.g. spironolactone) should not be used with VETORYL Capsules as both drugs have the potential to inhibit aldosterone, increasing the likelihood of hyperkalemia.

HUMAN WARNINGS: Keep out of reach of children. Not for human use. Wash hands after use. Do not empty capsule contents and do not attempt to divide the capsules. Do not handle the capsules if pregnant or if trying to conceive. Trilostane is associated with teratogenic effects and early pregnancy loss in laboratory animals. In the event of accidental ingestion/overdose, seek medical advice immediately and take the labeled container with you.

PRECAUTIONS: Hypoadrenocorticism can develop at any dose of VETORYL Capsules. A small percentage of dogs may develop corticosteroid withdrawl syndrome within 10 days of starting treatment. Mitotane (o,p'-DDD) treatment will reduce adrenal function. Experience in foreign markets suggests that when mitotane therapy is stopped, an interval of at least one month should elapse before the introduction of VETORYL Capsules.
It is important to wait for both the recurrence of clinical signs consistent with hyperadrenocorticism, and a post-ACTH cortisol level of > 9.1 µg/dL (> 250 nmol/L) before treatment with VETORYL Capsules is initiated. Close monitoring of adrenal function is advised, as dogs previously treated with mitotane may be more responsive to the effects of VETORYL Capsules.
The use of VETORYL Capsules will not affect the adrenal tumor itself. The safe use of this drug has not been evaluated in lactating dogs and males intended for breeding.

ADVERSE REACTIONS: The most common adverse reactions reported are poor/reduced appetite, vomiting, lethargy/dullness, diarrhea, elevated liver enzymes, elevated potassium with or without decreased sodium, elevated BUN, decreased Na/K ratio, weakness, elevated creatinine, shaking and renal insufficiency. Occasionally, more serious reactions, including severe depression, hemorrhagic diarrhea, collapse, hypoadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death. **Owners should be advised to discontinue VETORYL Capsules and contact their veterinarian immediately in the event potential drug intolerance is observed.**

Approved by FDA under NADA # 141-291

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As with all drugs, side effects may occur. In field studies and post-approval experience, the most common side effects reported were: anorexia, lethargy/depression, vomiting, diarrhea, elevated liver enzymes, elevated potassium with or without decreased sodium, elevated BUN, decreased Na/K ratio, hypoadrenocorticism, weakness, elevated creatinine, shaking, and renal insufficiency. In some cases, death has been reported as an outcome of these adverse events. VETORYL Capsules are not for use in dogs with primary hepatic or renal disease, or in pregnant dogs. Refer to the prescribing information for complete details or visit dechra-us.com.

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See page 43 for product information summary.

Impact of Feline Onychectomy Bans

Zenithson Ng, DVM, MS, DABVP (Canine & Feline Practice)
University of Tennessee

In the literature

Ellis A, van Haaften K, Protopopova A, Gordon E. Effect of a provincial feline onychectomy ban on cat intake and euthanasia in a British Columbia animal shelter system. *J Feline Med Surg*. 2022;24(8):739-744. doi:10.1177/1098612X211043820

THE RESEARCH ...

Feline onychectomy (ie, declawing) is controversial and presents an ethical dilemma. Pet owners may request declawing to prevent or manage destructive scratching behaviors, but patient welfare with elective amputation of digits should be considered. Refusal to perform the procedure and instead attempting to manage unwanted behaviors can result in frustrated owners choosing to euthanize or relinquish destructive cats. As more municipalities prohibit onychectomy, it is critical to understand and acknowledge the implications.

This study compared rates of and reasons for relinquishment and owner-requested euthanasia at multiple shelters in a single province in Canada 3 years before and 3 years after a legislative ban on onychectomy. The study aimed to determine whether the rate of relinquishment and euthanasia increased, as well as whether relinquishment increased due to destructive behavior.

Results demonstrated no significant difference in relinquishment or owner-requested euthanasia. Destructive behavior was an uncommon primary reason for surrender, comprising only 0.18% of surrendered cats over the study period; there was no significant increase after the ban. This may suggest most owners are able to manage or accept scratching behaviors, and withholding the option to declaw is unlikely to increase relinquishment or euthanasia; however, the study did not include cats that may have been declawed illegally, rehomed privately or through alternative welfare organizations, or released outside by owners because of unwanted scratching behaviors.

Future research should investigate whether owners who surrendered or euthanized cats due to destructive scratching would have pursued onychectomy if available, as owners of these cats may not have been committed to declawing, lessening justification of the procedure.

... THE TAKEAWAYS

Key pearls to put into practice:

1. Scratching is natural behavior in cats. New cat owners should be educated to expect this behavior and understand early management interventions.
2. There are short- and long-term welfare concerns with onychectomy, regardless of method or pain medication administered. Recently graduated clinicians are unlikely to be confident and able to perform this procedure as it continues to be removed from veterinary curricula. Hospitals will likely rely on experienced clinicians to perform the procedure or teach new practitioners willing to learn.
3. Relinquishment is usually related to owner concerns (eg, housing, financial challenges). Access to veterinary care and pet friendly housing are critical for preventing unnecessary relinquishment and euthanasia.

Suggested Reading

AAFP position statement: declawing. *J Feline Med Surg*. 2017;19(9):NP1-NP3. doi:10.1177/1098612X17729246

Martell-Moran NK, Solano M, Townsend HG. Pain and adverse behavior in declawed cats. *J Feline Med Surg*. 2018;20(4):280-288. doi:10.1177/1098612X17705044

Wilson DV, Pascoe PJ. Pain and analgesia following onychectomy in cats: a systematic review. *Vet Anaesth Analg*. 2016;43(1):5-17. doi:10.1111/vaa.12314

Research Note: **Impact of Music on Stress in Hospitalized Cats**

This study evaluated the effect of 2 types of music (ie, cat-specific, classical) compared with no music (control) on stress in hospitalized cats. Cat-specific songs used frequencies similar to cat vocal ranges and were composed to create an affiliative effect using pulses related to purring (1380 bpm) and suckling (250 bpm).[1]

Client-owned cats (n = 35) were randomly divided into 3 groups. Cat stress score, respiratory rate, and social interaction were measured at 5 specified times over 31 hours of hospitalization. Saliva for salivary cortisol measurement was collected during the first and fourth assessments.

Cat stress scores did not differ among the groups at any time point. A higher percentage of social interactions was noted in the cat-specific music group compared with the other groups at the first evaluation, and average respiratory rate was lower in the classical music group than in the control group on the fourth evaluation. Statistical analysis of salivary cortisol was not possible due to the small number of viable samples obtained. The authors concluded that both cat-specific and classical music appear to offer some benefit to hospitalized cats.

Reference

1. Snowdon CT, Teie D, Savage M. Cats prefer species-appropriate music. *Appl Anim Behav Sci*. 2015;166:106-111. doi:10.1016/j.applanim.2015.02.012

Source

Paz JE, da Costa FV, Nunes LN, Monteiro ER, Jung J. Evaluation of music therapy to reduce stress in hospitalized cats. *J Feline Med Surg*. 2022;24(10):1046-1052. doi:10.1177/1098612X211066484

CLARO®
(florfenicol, terbinafine, mometasone furoate)
Otic Solution for use in dogs only

Do Not Use in Cats.

Antibacterial, antifungal, and anti-inflammatory
For Otic Use in Dogs Only

See full product insert for complete prescribing information, 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.

DESCRIPTION: CLARO® contains 16.6 mg/mL florfenicol, 14.8 mg/mL terbinafine (equivalent to 16.6 mg/mL terbinafine hydrochloride) and 2.2 mg/mL mometasone furoate. Inactive ingredients include purified water, propylene carbonate, propylene glycol, ethyl alcohol, and polyethylene glycol.

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

DOSAGE AND ADMINISTRATION:
CLARO® should be administered by veterinary personnel.
Wear eye protection when administering CLARO®.
(see **Human Warnings, PRECAUTIONS, POST APPROVAL EXPERIENCE).**
Splatter may occur if the dog shakes its head following administration. Persons near the dog during administration should also take steps to avoid ocular exposure.
Shake before use.
Verify the tympanic membrane is intact prior to administration. (see **CONTRAINDICATIONS, PRECAUTIONS, POST APPROVAL EXPERIENCE).**
Administer one dose (1 dropperette) per affected ear.

1. Clean and dry the external ear canal before administering the product.
2. Verify the tympanic membrane is intact prior to administration.
3. Remove single dose dropperette from the package.
4. While holding the dropperette in an upright position, remove the cap from the dropperette.
5. Turn the cap over and push the other end of the cap onto the tip of the dropperette.
6. Twist the cap to break the seal and then remove cap from the dropperette.
7. Screw the applicator nozzle onto the dropperette.
8. Insert the tapered tip of the dropperette into the affected external ear canal and squeeze to instill the entire contents (1 mL) into the affected ear.
9. Gently massage the base of the ear to allow distribution of the solution. **Restrain the dog to minimize post application head shaking** to reduce potential for splatter of product and accidental eye exposure in people and dogs **(**see **POST APPROVAL EXPERIENCE)**.
10. Repeat with other ear as prescribed.
11. The duration of the effect should last 30 days. Cleaning the ear after dosing may affect product effectiveness.

CONTRAINDICATIONS:
Do not use in dogs with known tympanic membrane perforation (see **PRECAUTIONS**). CLARO® is contraindicated in dogs with known or suspected hypersensitivity to florfenicol, terbinafine hydrochloride, or mometasone furoate.

WARNINGS:
Human Warnings: **CLARO® may cause eye injury and irritation (**see **PRECAUTIONS, POST APPROVAL EXPERIENCE).** If contact with eyes occurs, flush copiously with water for at least 15 minutes. If irritation persists, contact a physician. Humans with known hypersensitivity to any of the active ingredients in CLARO® should not handle this product.

PRECAUTIONS:
For use in dogs only. Do not use in cats (see **POST APPROVAL EXPERIENCE)**.
Wear eye protection when administering CLARO® and restrain the dog to minimize post application head shaking. Reducing the potential for splatter of product will help prevent accidental eye exposure in people and dogs and help to prevent ocular injury (see **DOSAGE AND ADMINISTRATION, Human Warnings, POST APPROVAL EXPERIENCE)**.
Proper patient selection is important when considering the benefits and risks of using CLARO®. The integrity of the tympanic membrane should be confirmed before administering the product. CLARO® has been associated with rupture of the tympanic membrane. Reevaluate the dog if hearing loss or signs of vestibular dysfunction are observed during treatment. Signs of internal ear disease such as head tilt, vestibular signs, ataxia, nystagmus, facial paralysis, and keratoconjunctivitis sicca have been reported (see **POST APPROVAL EXPERIENCE)** with the use of CLARO®.
Do not administer orally.
Use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs **(**see **ANIMAL SAFETY).**
Use with caution in dogs with impaired hepatic function **(**see **ANIMAL SAFETY).**
The safe use of CLARO® in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

ADVERSE REACTIONS:
In a field study conducted in the United States (see **EFFECTIVENESS**), there were no directly attributable adverse reactions in 146 dogs administered CLARO®. **POST APPROVAL EXPERIENCE (2019)**: The following adverse events are based on post-approval adverse drug experience reporting for CLARO®. 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.
In **humans**, accidental exposure leading to corneal ulcers and other ocular injuries such as eye irritation and redness have been reported. Exposure occurred when the dog shook its head after application of CLARO®. Skin irritation has also been reported. In **dogs**, the adverse events reported are presented below in decreasing order of reporting frequency: Ear discharge, head shaking, ataxia, internal ear disorder (head tilt and vestibular), deafness, emesis, nystagmus, pinnal irritation and ear pain, keratoconjunctivitis sicca, vocalization, corneal ulcer, cranial nerve disorder (facial paralysis), tympanic membrane rupture.
CLARO® is not approved for use in **cats**. The adverse events reported following extra-label use in **cats** are presented below in decreasing order of reporting frequency: Ataxia, anorexia, internal ear disorder (head tilt and vestibular), Horner's syndrome (third eyelid prolapse and miosis), nystagmus, lethargy, anisocoria, head shake, emesis, tympanic rupture, and deafness.
To report suspected adverse drug events and/or obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, contact Elanco at 1-800-422- 9874.
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 Dog Owners:
Owners should be aware that adverse reactions may occur following administration of CLARO® and should be instructed to observe the dog for signs such as ear pain and irritation, vomiting, head shaking, head tilt, incoordination, eye pain and ocular discharge (see **POST APPROVAL EXPERIENCE**). Owners should be advised to contact their veterinarian if any of the above signs are observed. Owners should also be informed that splatter may occur if the dog shakes its head following administration of CLARO® which may lead to ocular exposure. Eye injuries, including corneal ulcers, have been reported in humans and dogs associated with head shaking and splatter following administration. Owners should be careful to avoid ocular exposure (see **PRECAUTIONS, POST APPROVAL EXPERIENCE**)

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

Important Safety Information:
Do Not Use in Cats. CLARO should be administered by veterinary personnel. **Wear eye protection when administering CLARO.** Restrain the dog to minimize post application head shaking to reduce potential for splatter of product and accidental eye exposure in people and dogs. Do not use in dogs with known tympanic membrane perforation. CLARO has been associated with rupture of the tympanic membrane. Owners should be made aware that adverse reactions may occur following administration of CLARO and splatter may occur if the dog shakes its head following administration. If contact with eyes occurs, flush copiously with water for at least 15 minutes. Please see accompanying brief summary for product safety information.

[1]Elanco Animal Health. Sales data on file.
[2]Angus JC. Otic cytology in health and disease. VCSA. 2004;34:411-24.

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See page 46 for product information summary.

Sports Ball Projectile Ocular Injuries in Dogs

Shannon D. Boveland, DVM, MS, DACVO
Auburn University

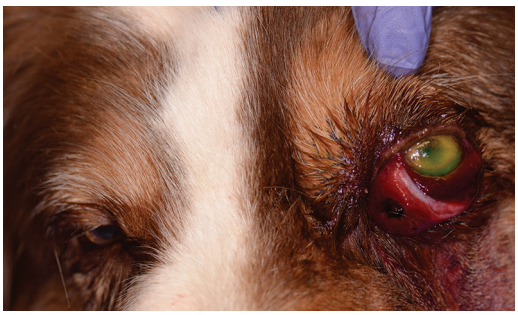
In the literature

Chan RX, Ledbetter EC. Sports ball projectile ocular trauma in dogs. *Vet Ophthalmol*. 2022;25(5):338-342. doi:10.1111/vop.12987

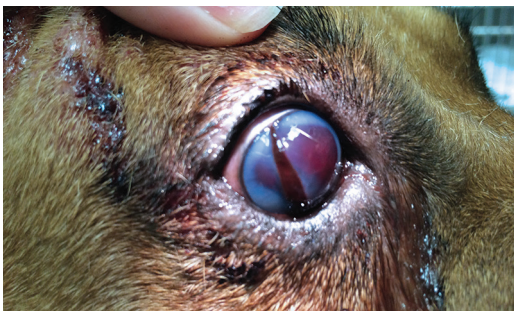
THE RESEARCH ...

Ocular trauma is common in dogs, and all ocular structures are vulnerable to injury after trauma to the eye. Some injuries (eg, iris rupture) may cause few effects, but more extensive lesions (eg, glaucoma, retinal detachment) can result in a nonfunctional eye. Uveitis is common with ocular trauma and should be aggressively managed to prevent complications.[1] Limited studies have reported eye injuries (eg, retinal detachment, hyphema) secondary to blunt and penetrating forces (eg, gunshots, cat clawing, bomb explosions).[2-4]

This retrospective study described prognostic indicators and visual outcomes of dogs with sports ball projectile ocular injuries. Closed-globe injuries (n = 12) were more common than open-globe injuries (n = 6); were commonly presented with traumatic uveitis, hyphema, and subconjunctival hemorrhage; and were medically



▲ **FIGURE 1** Hemorrhagic periocular discharge, elevated third eyelid with extensive conjunctival hemorrhage, severe chemosis, uveitis with marked miosis, and a superficial corneal ulcer stained with fluorescein seen in an 8-year-old spayed Australian shepherd with closed globe blunt trauma to the left eye. *Image courtesy of Auburn University*



▲ **FIGURE 2** Periocular serous discharge, extensive deep corneal edema, and hyphema seen in a dog with an open-globe, full-length vertical corneal laceration secondary to blunt trauma. *Image courtesy of Auburn University*

managed. Vision was maintained in 67% of cases. Open-globe injuries included corneal lacerations and scleral rupture, and all affected eyes required enucleation except one, which was managed with corneal laceration repair and third eyelid flap placement prior to referral (vision was maintained).

Injuries from small, dense sports balls (eg, golf balls, baseballs) were associated with a guarded prognosis and required more aggressive medical management compared with injuries from lighter balls (eg, tennis balls, toy balls). Traumatic uveitis was the most common initial ocular lesion and had varying visual outcomes. Hyphema was the second most common initial ocular injury and carried a poorer visual prognosis than traumatic uveitis.

… THE TAKEAWAYS

Key pearls to put into practice:

1. Compared with trauma from lighter sports balls, ocular trauma from small, dense sports balls typically results in more extensive injury and more frequent initial presence of hyphema and is often associated with enucleation or a poor visual prognosis.
2. Open-globe injuries have a poor visual prognosis and often result in enucleation.
3. Ocular ultrasound and CT scans can help identify vitreal hemorrhage, retinal detachment, retinal hemorrhage, scleral rupture, and orbital wall fractures that may not be clinically evident.

References

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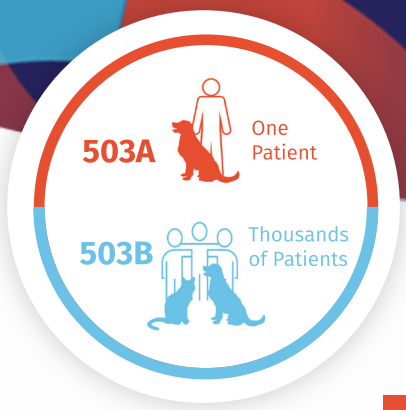
2. Sansom J, Labruyère J. Penetrating ocular gunshot injury in a Labrador retriever. *Vet Ophthalmol*. 2012;15(2):115-122. doi:10.1111/j.1463-5224.2011.00941.x
3. Mitchell N. Cat claw injuries in canine and feline corneas. *UK Vet Companion Animal*. 2008;13(9):59-67. doi:10.1111/j.2044-3862.2008.tb00541.x
4. Shelah M, Weinberger D, Ofri R. Acute blindness in a dog caused by an explosive blast. *Vet Ophthalmol*. 2007;10(3):196-198. doi:10.1111/j.1463-5224.2007.00533.x



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Talk to your Merck Animal Health representative to learn more.

IMPORTANT SAFETY INFORMATION:

BRAVECTO (fluralaner) Chews for Dogs. The most commonly reported adverse reactions include vomiting, decreased appetite, diarrhea, lethargy, polydipsia, and flatulence. **BRAVECTO Chews** has not been shown to be effective for 12-weeks' duration in puppies less than 6 months of age. **BRAVECTO Chews** is not effective against lone star ticks beyond 8 weeks of dosing. Fluralaner 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. For full prescribing information, please see page 52.

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 microfi lariae. Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention. For full prescribing information, please see page 53.

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MERCK
Animal Health

BRAVECTO® (fluralaner) Chews

Flavored chews for dogs.

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

Description:
Each chew is formulated to provide a minimum dose of 11.4 mg/lb (25 mg/kg) body weight.

The chemical name of fluralaner is (±)-4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-methyl-*N*-[2-oxo-2-(2,2,2-trifluoroethylamino) ethyl]benzamide.

Indications:
Bravecto kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

Bravecto is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

Dosage and Administration:
Bravecto should be administered orally as a single dose every 12 weeks according to the **Dosage Schedule** below to provide a minimum dose of 11.4 mg/lb (25 mg/kg) body weight.

Bravecto may be administered every 8 weeks in case of potential exposure to *Amblyomma americanum* ticks (see **Effectiveness**).

Bravecto should be administered with food.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner Content (mg)	Chews Administered
4.4 – 9.9	112.5	One
>9.9 – 22.0	250	One
>22.0 – 44.0	500	One
>44.0 – 88.0	1000	One
>88.0 – 123.0*	1400	One

*Dogs over 123.0 lb should be administered the appropriate combination of chews

Treatment with Bravecto may begin at any time of the year and can continue year round without interruption.

Contraindications:
There are no known contraindications for the use of the product.

Warnings:
Not for human use. Keep this and all drugs out of the reach of children. Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. Do not eat, drink or smoke while handling the product. Wash hands thoroughly with soap and water immediately after use of the product.

Keep Bravecto in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions:
Fluralaner 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.

Bravecto has not been shown to be effective for 12-weeks duration in puppies less than 6 months of age. Bravecto is not effective against *Amblyomma americanum* ticks beyond 8 weeks after dosing (see **Effectiveness**).

Adverse Reactions:
In a well-controlled U.S. field study, which included 294 dogs (224 dogs were administered Bravecto every 12 weeks and 70 dogs were administered an oral active control every 4 weeks and were provided with a tick collar); there were no serious adverse reactions. All potential adverse reactions were recorded in dogs treated with Bravecto over a 182-day period and in dogs treated with the active control over an 84-day period. The most frequently reported adverse reaction in dogs in the Bravecto and active control groups was vomiting.

Percentage of Dogs with Adverse Reactions in the Field Study

Adverse Reaction (AR)	Bravecto Group: Percentage of Dogs with the AR During the 182-Day Study (n=224 dogs)	Active Control Group: Percentage of Dogs with the AR During the 84-Day Study (n=70 dogs)
Vomiting	7.1	14.3
Decreased Appetite	6.7	0.0
Diarrhea	4.9	2.9
Lethargy	5.4	7.1
Polydipsia	1.8	4.3
Flatulence	1.3	0.0

In a well-controlled laboratory dose confirmation study, one dog developed edema and hyperemia of the upper lips within one hour of receiving Bravecto. The edema improved progressively through the day and had resolved without medical intervention by the next morning.

Post Approval Experience (2019):
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 fluralaner:

Vomiting, lethargy, diarrhea (with and without blood), anorexia, pruritis, polydipsia, seizure, allergic reactions (including hives, swelling, erythema), dermatitis (including crusts, pustules, rash), tremors and ataxia.

Contact Information:
To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Merck Animal Health at 1-800-224-5318. Additional information can be found at www.bravecto.com.

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:
Peak fluralaner concentrations are achieved between 2 hours and 3 days following oral administration, and the elimination half-life ranges between 9.3 to 16.2 days. Quantifiable drug concentrations can be measured (lower than necessary for effectiveness) through 112 days. Due to reduced drug bioavailability in the fasted state, fluralaner should be administered with food.

Mode of Action:
Fluralaner is for systemic use and belongs to the class of isoxazoline-substituted benzamide derivatives. Fluralaner is an inhibitor of the arthropod nervous system. The mode of action of fluralaner is the antagonism of the ligand-gated chloride channels (gamma-aminobutyric acid (GABA)-receptor and glutamate-receptor).

Effectiveness:
Bravecto began to kill fleas within two hours after administration in a well-controlled laboratory study. In a European laboratory study, Bravecto killed fleas and *Ixodes ricinus* ticks and reduced the numbers of live fleas and *Ixodes ricinus* ticks on dogs by > 98% within 12 hours for 12 weeks. In a well-controlled laboratory study, Bravecto demonstrated 100% effectiveness against adult fleas 48 hours post-infestation for 12 weeks. In well-controlled laboratory studies, Bravecto demonstrated ≥ 93% effectiveness against *Dermacentor variabilis*, *Ixodes scapularis* and *Rhipicephalus sanguineus* ticks 48 hours post-infestation for 12 weeks. Bravecto demonstrated ≥90% effectiveness against *Amblyomma americanum* 72 hours post-infestation for 8 weeks, but failed to demonstrate ≥90% effectiveness beyond 8 weeks.

In a well-controlled U.S. field study, a single dose of Bravecto reduced fleas by ≥ 99.7% for 12 weeks. Dogs with signs of flea allergy dermatitis showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as a direct result of eliminating flea infestations.

Palatability: In a well-controlled U.S. field study, which included 559 doses administered to 224 dogs, 80.7% of dogs voluntarily consumed Bravecto within 5 minutes, an additional 12.5% voluntarily consumed Bravecto within 5 minutes when offered with food, and 6.8% refused the dose or required forced administration.

Animal Safety:
Margin of Safety Study: In a margin of safety study, Bravecto was administered orally to 8- to 9-week-old puppies at 1, 3, and 5X the maximum label dose of 56 mg/kg at three, 8-week intervals. The dogs in the control group (0X) were untreated.

There were no clinically-relevant, treatment-related effects on physical examinations, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, and urinalysis), gross pathology, histopathology, or organ weights. Diarrhea, mucoid and bloody feces were the most common observations in this study, occurring at a similar incidence in the treated and control groups. Five of the twelve treated dogs that experienced one or more of these signs did so within 6 hours of the first dosing. One dog in the 3X treatment group was observed to be dull, inappetant, with evidence of bloody diarrhea, vomiting, and weight loss beginning five days after the first treatment. One dog in the 1X treatment group vomited food 4 hours following the first treatment.

Reproductive Safety Study: Bravecto was administered orally to intact, reproductively- sound male and female Beagles at a dose of up to 168 mg/kg (equivalent to 3X the maximum label dose) on three to four occasions at 8-week intervals. The dogs in the control group (0X) were untreated.

There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs) or histopathology findings (adult dogs and puppies). One adult 3X treated dog suffered a seizure during the course of the study (46 days after the third treatment). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions).

The following abnormalities were noted in 7 pups from 2 of the 10 dams in only the treated group during gross necropsy examination: limb deformity (4 pups), enlarged heart (2 pups), enlarged spleen (3 pups), and cleft palate (2 pups). During veterinary examination at Week 7, two pups from the control group had inguinal testicles, and two and four pups from the treated group had inguinal and cryptorchid testicles, respectively. No undescended testicles were observed at the time of necropsy (days 50 to 71).

In a well-controlled field study Bravecto was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics, and steroids. No adverse reactions were observed from the concurrent use of Bravecto with other medications.

Storage Information:
Do not store above 86°F (30°C).

How Supplied:
Bravecto (fluralaner) is available in five strengths (112.5, 250, 500, 1000, and 1400 mg fluralaner per chew). Each chew is packaged individually into aluminum foil blister packs sealed with a peelable paper backed foil lid stock. Product may be packaged in 1, 2, or 4 chews per package.

Approved by FDA under NADA # 141-426

Distributed by:
Intervet Inc (d/b/a Merck Animal Health)
Madison, NJ 07940

Fluralaner (active ingred.) Made in Japan.
Formulated in Austria

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MERCK Animal Health

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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 ($C_{32}H_{46}NO_7$, 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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Peripheral Lymphadenopathy in Dogs

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Following are differential diagnoses for dogs presented with peripheral lymphadenopathy.

- Neoplastic
  - Lymphoproliferative
    - –Lymphoma
    - –Chronic lymphocytic leukemia
    - –Acute lymphoblastic leukemia
  - Metastatic neoplasia (common causes)
    - –Carcinoma (eg, mammary gland carcinoma, thyroid carcinoma, oral squamous cell carcinoma)
    - –Sarcoma (eg, soft tissue sarcoma, histiocytic sarcoma)
    - –Mast cell tumor
    - –Melanoma (oral or digit)
- Reactive
  - Infectious
    - –Systemic fungal infection
      - Blastomycosis (ie, *Blastomyces dermatitidis*)
      - Histoplasmosis (ie, *Histoplasma capuslatum*)
      - Coccidioidomycosis (ie, *Coccidioides immitis*)
      - Sporotrichosis (ie, *Sporothrix schenckii*)
      - Aspergillosis (eg, *Aspergillus fumigatus, A flavus*)
      - Pythiosis (ie, *Pythium insidiosum*)
    - –Bacterial infection
      - Brucellosis (ie, *Brucella canis*)
      - Nocardiosis (ie, *Nocardia* spp)
      - Plague (ie, *Yersinia pestis*)
    - –Vector-borne disease (coinfection is common)
      - Ehrlichiosis (eg, *Ehrlichia canis, E chaffeensis, E ewingi, E equi*)
      - Anaplasmosis (ie, *Anaplasma phagocytophilum*)
      - Neorickettsiosis (ie, *Neorickettsia risticii*)
      - Salmon poisoning disease (ie, *Neorickettsia helminthoeca*)
      - Bartonellosis (eg, *Bartonella henselae*,[1] *B clarridgeiae*, *B vinsonii*)
      - Rocky Mountain spotted fever (ie, *Rickettsia rickettsii*)
      - Leishmaniasis (eg, *Leishmania infantum, L donovani*)
      - Babesiosis (ie, *Babesia canis*)
      - Hepatozoonosis (ie, *Hepatozoon americanum*)
  - Severe generalized pyoderma
    - –Primary bacterial pyoderma
    - –Secondary bacterial pyoderma
      - Atopy
      - Demodectic mange
      - Sarcoptic mange
      - Sebaceous adenitis
- Inflammatory, noninfectious
  - Cutaneous lupus erythematosus[2]
  - Juvenile-onset sterile granulomatous dermatitis and lymphadenitis (ie, juvenile cellulitis, puppy strangles)
  - Adult-onset sterile granulomatous dermatitis and lymphadenitis (ie, juvenile cellulitis)[3]
- Other
  - Phenobarbital-induced pseudolymphoma[4]

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Escherichia coli in Dogs & Cats

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Microbiology

Escherichia coli is a gram-negative bacterium in the Enterobacterales order and is commonly found in the GI tract and the environment. Strains are mostly nonpathogenic but can be opportunistic. Pathogenicity is largely related to a range of virulence genes, including those that influence the ability of the bacterium to adhere to tissue or produce toxins. *E coli* can be classified into groups (including enteropathogenic, enterotoxigenic, enterohemorrhagic, adherent invasive, and uropathogenic) based on the presence of various virulence mechanisms. Similar to other gram-negative bacteria, cell walls of *E coli* contain endotoxin, a pyrogenic toxin that can be associated with severe disease (eg, septic shock).

Although many genetic lineages and strains of *E coli* can be found in dogs and cats,[1,2] some strains are shared among dogs, cats, and humans.[1,3] Clinically relevant transmission between species should thus not be ignored.

Diseases of Small Animals

E coli can cause opportunistic infections in any body system (see ***Table 1***, next page) but is most commonly involved in urinary tract and skin/soft tissue infections.

Diagnosis

Diagnosis requires detection of *E coli* at an infected site, primarily via culture. Definitive diagnosis is likely in cases in which *E coli* is isolated from a normally sterile site (eg, blood) or *E coli* is found at sites where it is not normally present and there are supportive clinical and cytologic findings (eg, isolation from the lower airways in a patient with septic changes on bronchoalveolar lavage cytology). Although *E coli* is the leading cause of bacterial cystitis, this bacterium can also be found in patients without classical clinical signs of lower urinary tract disease (ie, subclinical bacteriuria), making interpretation of culture and susceptibility results challenging.[4-9] Clinical signs and other urinalysis results are important for determining the clinical relevance of *E coli* isolation.

Enteric disease is the most challenging to diagnose, as *E coli* is a common enteric organism found in many healthy dogs. Detecting specific virulence factors may be useful, but the range of potential virulence factors and diseases is not adequately understood, and *E coli* with disease-associated virulence genes can be found in healthy patients. Diagnosis of histiocytic ulcerative

TABLE 1

DISEASE EXAMPLES THAT CAN INVOLVE *ESCHERICHIA COLI*

System	Disease
Urogenital	Cystitis Pyelonephritis Prostatitis Pyometra
Respiratory	Pneumonia Pyothorax
Hepatobiliary	Cholangiohepatitis
Skin and soft tissue	Wound infections Cellulitis Necrotizing fasciitis
Blood	Sepsis
GI	Acute diarrhea Histiocytic ulcerative (granulomatous) colitis
Neurological	Meningitis
Musculoskeletal	Discospondylitis

There are no specific preventive measures for *E coli*, but some syndromes (eg, bacterial cystitis) are often associated with predisposing factors.

ESBL = extended spectrum beta-lactamase

colitis (ie, granulomatous colitis) typically relies on identification of intracellular *E coli* via fluorescent in situ hybridization.[10]

Treatment & Antimicrobial Resistance

E coli is intrinsically susceptible to a wide range of antimicrobials (***Table 2***), but acquired resistance and resistance from narrow spectrum beta-lactamase production are common.[11,12] Extended spectrum beta-lactamase (ESBL)–producing strains are increasingly common and confer resistance to cephalosporins; however, these strains often acquire numerous additional resistance genes, making them resistant to most available antimicrobials.[13,14] Fluoroquinolone resistance is also increasingly common. Clinical observation suggests ESBL-producing *E coli* are typically susceptible to a limited range of drugs, particularly amikacin and meropenem. Fosfomycin (dogs only) and nitrofurantoin can be used to treat bacterial cystitis caused by multidrug-resistant *E coli.* Further development of resistance is a concern with *E coli*. In human medicine, *E coli* is increasingly resistant to most antimicrobials, including carbapenems.

Treatment should ideally be based on culture and susceptibility results; however, empirical treatment may be indicated in lieu of or while waiting for culture and susceptibility results. Systemic antimicrobials can be withheld until culture results are available in some cases (eg, disease is very mild; anti-inflammatory drugs [eg, NSAIDs], topical treatment, or other supportive care might be effective). Culture importance depends on confidence in the diagnosis (ie, *E coli* is the likely pathogen), likelihood of antimicrobial resistance (potential for treatment failure), and implications of failed initial treatment (eg, prolonged mild disease vs life-threatening progression). Factors associated with increased risk for resistance include prior antimicrobial treatment, hospitalization, and feeding raw diets, including raw animal-based treats.[15-19]

Prevention

There are no specific preventive measures for *E coli*,

but some syndromes (eg, bacterial cystitis) are often associated with predisposing factors, treatment of which may reduce the risk for recurrent infection.

Zoonotic Risks

Although *E coli* is a common cause of infection in humans, zoonotic risks from companion animals are poorly understood. Overlap of strains in humans and companion animals is possible,[20-22] and presence of the same strain in humans and their pets has been reported.[23,24] Whether these overlaps reflect animal to human, human to animal, or common source infection is not well understood. Use of basic hygiene practices (eg, hand washing, avoiding contact with feces and infected sites) is prudent when handling infected patients.

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TABLE 2

COMMON ANTIMICROBIAL OPTIONS FOR *ESCHERICHIA COLI* INFECTIONS

Antimicrobial	Comment
Penicillins (amoxicillin/ampicillin)	Can be effective, but resistance from beta-lactamase production is not uncommon. Amoxicillin remains a first-line treatment choice for bacterial cystitis because of high drug levels in urine.
Amoxicillin/clavulanic acid	Can be effective against isolates producing narrow spectrum beta-lactamases, which likely account for the majority of *E coli* in most environments; however, efficacy against beta-lactamase–producing *E coli* in tissue (apart from bacterial cystitis) is controversial, and efficacy may be poorer than previously assumed
Cephalosporins	Activity against *E coli* increases with later generation drugs. Third-generation cephalosporins are excellent against *E coli* but should be reserved for situations in which lower tier drugs cannot be used. Although cefovecin is a third-generation cephalosporin, its activity against *E coli* is limited.
Fluoroquinolones	Excellent activity against *E coli* but should be reserved for situations in which lower tier drugs (eg, amoxicillin, amoxicillin/clavulanic acid, doxycycline, potentiated sulfonamides [eg, trimethoprim/sulfamethoxazole]) are not an option
Doxycycline	Often overlooked but can be effective; resistance is not uncommon
Aminoglycosides	Excellent activity against *E coli*, including most multidrug-resistant strains; typically reserved for isolates resistant to most other options (eg, ESBL-producing strains) due to parenteral administration and toxicity concerns
Carbapenems	Similar to aminoglycosides, carbapenems have activity against *E coli* (including most multidrug-resistant strains) and should be reserved for exceptional circumstances in which isolates are resistant to most other options (eg, ESBL-producing strains).
Nitrofurantoin	Can be useful for bacterial cystitis, as resistance is uncommon, even with multidrug-resistant strains; not effective for infections other than bacterial cystitis
Fosfomycin	Dogs only; most often used for multidrug-resistant bacterial cystitis; resistance is rare; can be used for other infections (unlike nitrofurantoin)
Potentiated sulfonamides	Potentially useful against *E coli*, especially for bacterial cystitis; resistance is not uncommon

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Therapy Protocols for Acute Hemorrhagic Diarrhea Syndrome in a Dog

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THE CASE

Rosie, a 4-year-old, 11-lb (5-kg) spayed Yorkshire terrier, is presented 12 hours after an episode of hematemesis followed by hemorrhagic diarrhea. She is hyporexic and increasingly lethargic. There is no known history of toxin exposure or dietary changes. Vaccinations, heartworm, and flea and tick preventives are current.

On presentation, Rosie is dull, tachycardic (180 bpm), and tachypneic (80 breaths per minute) with weak femoral pulses, pale pink mucous membranes, and a prolonged capillary refill time of 3 seconds. She is estimated to be 7% dehydrated. Rectal temperature is 99.1ºF (37.2ºC), and frank blood is present on the thermometer.

Physical examination findings suggest hypovolemic shock, and immediate stabilization measures are initiated. An IV catheter is placed, and a bolus of lactated Ringer's solution (LRS; 400 mL/hour [20 mL/kg IV over 15 minutes]) is administered with a fluid pump. The remainder of the physical examination is unremarkable except for mild abdominal discomfort without distension. Cardiothoracic auscultation is normal.

Abdominal radiograph and thoracic point-of-care ultrasound results are normal. Blood pressure measured via Doppler is 75 mm Hg. A blood gas and electrolyte panel reveal moderate metabolic acidosis with respiratory compensation and severe hyperlactatemia (***Table 1***, next page). Packed cell volume (PCV) and total solids (TS) are 65% and 5.5 g/dL, respectively. Electrocardiogram reveals sinus tachycardia.

What are the next steps?

THE CHOICE IS YOURS ...

CASE ROUTE 1

You suspect acute hemorrhagic diarrhea syndrome (AHDS), but the pet owner declines further diagnostics due to financial concerns and requests conservative treatment and supportive care (see page 60).

CASE ROUTE 2

You suspect acute hemorrhagic diarrhea syndrome (AHDS) and pursue further diagnostics (see page 61).

CASE ROUTE 1

You initiate conservative treatment and supportive care.

Case Progression

Resuscitation with LRS (20 mL/kg IV bolus) is performed. Rosie stabilizes, and her vital signs return to normal (heart rate, 120 bpm; respiratory rate, 24 breaths per minute; blood pressure measured via Doppler, 110 mm Hg). She is hospitalized overnight, and IV fluids are administered.

TABLE 1

SELECTED VALUES FROM THE BLOOD GAS & ELECTROLYTE PANEL

Value	Result	Reference Interval
PCV (%)	**65**	37-55
TS (g/dL)	5.5	5.4-7.1
pH	**7.25**	7.36 ± 0.02
Partial pressure of carbon dioxide (mm Hg)	**30**	43 ± 3
Base deficit (mmol/L)	**-3**	–1 ± 1
Bicarbonate (mmol/L)	**16**	23 ± 1
Lactate (mmol/L)	**5.6**	0.5-2
Potassium (mEq/L)	4.8	3.9-4.9
Sodium (mEq/L)	142	140-150
Chloride (mEq/L)	111	109-120
Glucose (mg/dL)	72	65-112

Values outside the reference interval are bold.

AHDS = acute hemorrhagic diarrhea syndrome
LRS = lactated Ringer's solution
PCV = packed cell volume
TS = total solids

Fluid therapy comprises maintenance (12.5 mL/hour) and rehydration over 12 hours (350 mL dehydration deficit). Maropitant (1 mg/kg IV once) and pantoprazole (1 mg/kg IV once) are also administered. The patient is bright and adequately hydrated the following morning.

Rosie is discharged, and the owner is counseled to return to an emergency clinic if she shows inappetence for >24 hours, is dull and lethargic, or has pale gums. Omeprazole (1 mg/kg PO every 12 hours for 3 days) and maropitant (2 mg/kg PO every 24 hours for 3 days) are prescribed. The owner is instructed on how to administer LRS (30 mL/kg/24 hours SC as needed; total, 150 mL) if Rosie is unwilling to drink and has a significant amount of diarrhea. Probiotics containing multiple live bacterial strains and a bland diet are also recommended.

Clinical Considerations

AHDS is the sudden onset of severe bloody diarrhea with significant loss of fluid into the intestinal lumen.[1] This condition was previously known as *hemorrhagic gastroenteritis*, but a study showed no evidence of histopathologic lesions in the stomach.[2] The exact etiology of AHDS is unknown and is likely multifactorial. *Clostridium perfringens* has been suspected as a cause but can also be found in the stool of healthy dogs; most *C perfringens* biotypes are not enteropathogenic. *C perfringens* can, however, produce virulence factors that contribute to their pathogenicity.[3] Recent evidence suggests type A *C perfringens* may play a significant role in the pathogenesis of AHDS due to production of the pore-forming toxin NetF[4,5]; however, a noninvasive test to definitively diagnose AHDS does not currently exist. Diagnosis is based on clinical suspicion and exclusion of other causes of hemorrhagic diarrhea.

This patient's signalment (ie, young to middle-aged small breed dog), history (ie, peracute onset of hematemesis followed by hemorrhagic diarrhea), and elevated PCV raised suspicion for AHDS.[1,6] Elevated PCV occurs due to hemoconcentration, and concurrent loss of proteins in the GI tract results

in low to normal total protein concentration. AHDS is characterized by increased vascular and GI mucosal permeability, leading to a rapid loss of fluid, electrolytes, and protein in the intestines and possible severe dehydration and hypovolemic shock.[7]

No specific therapy for AHDS is available, and the suggested treatment is aggressive fluid therapy and supportive care. Antibiotics do not improve clinical outcome or recovery time in nonseptic patients, despite likelihood of bacterial etiology.[8,9] Disruption of the GI mucosal barrier may predispose the patient to bacterial translocation, but one study suggested there may be no significant difference in incidence of bacteremia between dogs with AHDS and healthy dogs.[10] Unwarranted antimicrobial use should be avoided to reduce the risk for antibiotic resistance and intestinal dysbiosis. In addition, antimicrobials may increase toxin release; in humans with Shiga-toxin–producing *Escherichia coli*, for example, antibiotic treatment can stimulate toxin release although there is unclear evidence supporting antimicrobial safety and efficacy.[11]

Severe intestinal mucosal damage, barrier dysfunction, and bacterial dysbiosis may be important in the pathophysiology of AHDS. Early enteral nutrition, dietary fiber, and probiotics can help restore the bacterial microbiome and intestinal barrier.[1] Probiotic treatment may be associated with an accelerated normalization of the intestinal microbiome and a shortened clinical course.[12] Although probiotics have been shown not to have a significant impact, they are unlikely to cause harm.[13]

Outcome

Rosie is anorexic over the next 24 hours, but gradually regains her normal appetite over the next 72 hours.

Choice Implications

AHDS can be fatal if untreated. Most dogs that receive aggressive therapy improve rapidly in 24 to 48 hours.[6,8] Outpatient therapy is not recommended, but minimal diagnostics and minimal hospitalization may be considered if there are financial concerns and the patient responds well to initial fluid resuscitation.

In humans, acute enteritis can trigger chronic GI disease; this may also occur in dogs.[14,15] Owners should be instructed to closely monitor for chronic or intermittent GI signs.

CASE ROUTE 2

The patient does not respond well to initial resuscitation. You pursue further diagnostics to rule out other underlying disease processes, and you administer more intensive treatment during hospitalization.

Case Progression

Initial resuscitation with LRS (20 mL/kg IV over 15 minutes) is performed. Rosie improves, but her vitals are still abnormal (heart rate, 150 bpm; respiratory rate, 52 breaths per minute; light pink mucous membranes with a capillary refill time of 2 seconds). A second bolus of LRS (20 mL/kg/15 minutes) is given. Despite mild improvement, she is still tachycardic with low to normal blood pressure (90 mm Hg) measured via Doppler. LRS (120 mL/kg/day or 25 mL/hour) is continued.

Further diagnostics are performed to rule out other underlying causes for hemorrhagic diarrhea. CBC shows moderate leukocytosis characterized by neutrophilia with 5% band neutrophil concentration, hemoconcentration, and a normal platelet count.

Serum chemistry profile reveals a mild to moderate ALT elevation, mildly elevated BUN and creatinine, and severely decreased albumin (1.4 g/dL). Urinalysis reveals concentrated urine (specific gravity, 1.045); no other abnormalities are present. Basal cortisol (14 µg/dL) is elevated. Abdominal ultrasonography is performed by a board-certified radiologist; results show fluid-distended loops of intestine with no other abnormalities. A GI PCR panel for *Giardia* spp, *Cryptosporidium* spp, *Salmonella* spp, *Clostridium perfringens* enterotoxin A gene, canine enteric coronavirus, canine parvovirus 2, and canine distemper virus is ordered, but results will not be available for several days. A quantitative serum canine pancreatic lipase immunoreactivity is also performed.

After LRS (25 mL/hour) has been administered for 2 hours, PCV and TS decreased to 40% and 2.5 g/dL, respectively, canine albumin (0.8 g/kg, diluted to 5% over 6 hours; total, 4 g) is administered. Vital signs return to normal, but mentation is still dull. Heart rate is 120 bpm, respiratory rate is 24 breaths per minute, and blood pressure measured via Doppler is 110 mm Hg.

There is cardiovascular stability and adequate hydration after albumin transfusion. Hypoproteinemia-associated interstitial edema is a concern; therefore, crystalloid fluid therapy should be closely monitored. Maintenance IV fluids (12.5 mL/hour) will be continued. The fluid rate can be increased if there are significant losses (via diarrhea and vomiting). Frequently weighing the patient, urine, and feces can help guide fluid therapy.

AHDS = acute hemorrhagic diarrhea syndrome
LRS = lactated Ringer's solution
PCV = packed cell volume
TS = total solids

Ampicillin/sulbactam (30 mg/kg IV every 8 hours), maropitant (1 mg/kg IV every 24 hours), pantoprazole (1 mg/kg IV every 12 hours), and buprenorphine (0.02 mg/kg IV every 8 hours) are administered. A nasogastric feeding tube is placed, and a liquid GI diet (one-third of the resting energy requirement per day) is administered via CRI and gradually increased over the next few days. The most common commercially available diet is a highly digestible, low-fat liquid diet.

Clinical Considerations

This patient did not respond rapidly to initial resuscitation; therefore, further diagnostics were performed to rule out other underlying causes of hemorrhagic diarrhea and vomiting. CBC results ruled out thrombocytopenia as a cause of GI bleeding. Hypoadrenocorticism was unlikely due to significant neutrophilia and elevated baseline cortisol. Kidney values were mildly elevated, and the urine was concentrated; therefore, azotemia was most likely prerenal in origin, and GI signs were not a result of kidney failure. Liver failure was unlikely because only ALT was moderately elevated, which was likely related to hypoperfusion of the liver. Abdominal ultrasonography was used to rule out obstruction, intussusception, and mesenteric volvulus as causes for GI signs and hypovolemia and to evaluate the pancreas while quantitative canine pancreatic lipase immunoreactivity assay results were pending. GI PCR panel ruled out infectious causes of diarrhea. A diagnosis of AHDS was most likely after other causes for hemorrhagic diarrhea and shock were excluded.

Patients with AHDS commonly have signs (eg, hypovolemia due to rapid fluid loss) of systemic inflammatory response syndrome (***Table 2***).[10] Determining whether patients are also septic can be challenging. Most patients with AHDS do not require antimicrobials, but some can become septic and should be rapidly identified. A defined a set of criteria that justify the use of antimicrobials in patients with AHDS is available (see ***Criteria for Antibiotic Administration in Septic Patients with Acute Hemorrhagic Diarrhea Syndrome***).[1]

Potentiated penicillins (eg, ampicillin/sulbactam, amoxicillin/clavulanic acid) are often administered as a first-line treatment for AHDS because of their broad-spectrum activity against gram-positive and gram-negative bacteria, including *Clostridium* spp.[8,9] Metronidazole may have no additional benefit in nonseptic dogs with AHDS.[16]

Because the patient in this case had severe hypoproteinemia, a colloid solution (ie, canine albumin) was administered to continue resuscitation. Canine albumin increases serum albumin concentration, colloid osmotic pressure, and blood pressure in dogs with septic peritonitis.[17] Fresh frozen plasma can also be considered. Fresh frozen plasma contains ≈30 g/L of albumin, so larger volumes are necessary to significantly increase albumin concentration.[18]

This patient was started on early enteral nutrition, which has demonstrated clinical benefit in critically ill humans and some veterinary patients.[19-21] Enteral nutrition maintains the functional and structural integrity of the intestinal epithelium and stimulates intestinal contractility.[22]

Outcome

Rosie begins to eat on her own after 3 days in the hospital, and probiotics containing multiple live bacterial strains are administered with food. IV fluid therapy is gradually tapered over the next 24 hours. IV medications are switched to oral administration, and she is discharged after 4 days. Rosie continues to eat on her own at home. Seven days after initial presentation, all medications are stopped, and Rosie has full recovery.

Choice Implications

Most patients with AHDS have a good prognosis with intensive supportive care; however, hospitalization and close monitoring are recommended for patients that develop complications (eg, severe hypoalbuminemia, bacterial translocation/sepsis, disseminated intravascular coagulation).[1]

TABLE 2

CRITERIA FOR DIAGNOSIS OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME IN DOGS[23]

Parameter	Criteria
Temperature	Small dogs (<33 lb [15 kg]): <99.5°F (37.5°C) or >102.9°F (39.4°C) Medium to large dogs (≥33 lb [15 kg]): <99.5°F (37.5°C) or >102.7°F (39.3°C)
Heart rate	>140 bpm
Respiratory rate	>20 breaths per minute
WBC	<6 or >25 × 10^3/μL; >3% band neutrophil concentration

Diagnosis requires ≥2 criteria.

CRITERIA FOR ANTIBIOTIC ADMINISTRATION IN SEPTIC PATIENTS WITH ACUTE HEMORRHAGIC DIARRHEA SYNDROME

- Systemic signs of illness that persist after volume resuscitation and supportive care
  - Dull mentation
  - Tachycardia
  - Tachypnea
  - Hypotension
- Signs of systemic inflammation at presentation
  - Rectal temperature >103.1°F (39.5°C)
  - WBC <4,000/mL or >25,000/mL
  - Band neutrophil concentration >2,500/mL
- Immunocompromised
  - Immunosuppressive treatment
  - Neutropenia
- Suspected ineffective clearance of bacteria by the liver
  - Portosystemic shunt flow
  - Liver dysfunction

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FROM CLINICIAN'S BRIEF ON SOCIAL MEDIA

WE ASKED . . .

Have you treated a linear foreign body in a cat by cutting and allowing the string to pass?

"Yes, multiple times. Cats with linear foreign bodies are administered drugs used to treat hairballs and monitored. Sometimes laparotomy is needed, but most threads pass without issue if radiographs do not show plication of the small intestine." —*Ellen G*

"No; the cat almost lost its tongue the last time I let a string pass." —*Alberto A*

"I have done it twice successfully. The owner declined surgery, so cutting and allowing the string to pass was worth trying."—*Sarah F*

"We used this treatment when an owner could only afford IV fluids and hospitalization. We initiated treatment early, and no plication was visible on imaging. The cat recovered and was able to eat within 2 days." —*Christina C*

Do you administer acepromazine in dogs with a history of seizures?

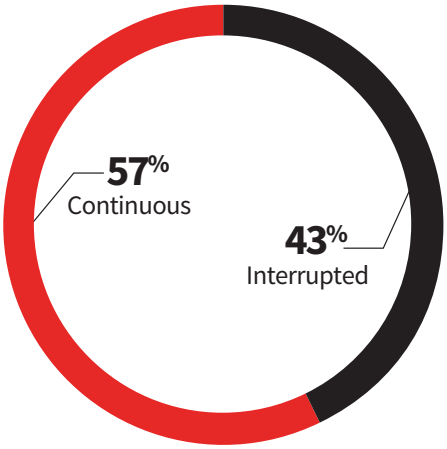
"I work in an intensive care unit and receive sedation plans from neurologists. Acepromazine is frequently used in conjunction with trazodone in patients with idiopathic epilepsy." —*Fiona W*

"I have not used acepromazine but would use it without hesitation, if indicated."—*Stephanie W*

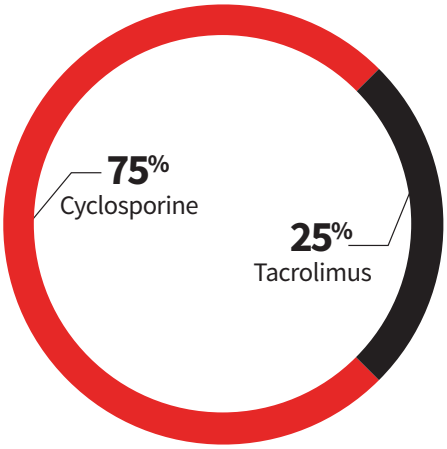
"Yes; I have used it for years in conjunction with other medications (eg, levetiracetam, diazepam). Acepromazine works especially well in dogs with bufo toad poisoning and lowers body temperature if the patient is hyperthermic."—*Jitka M*

"I use acepromazine if there is no suspicion of elevated intracranial pressure."—*Ellen W*

Which suture technique do you use when closing a linea?



Which lacrostimulant do you typically use to treat keratoconjunctivitis sicca?



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Heartgard® PLUS (ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal 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 roundworms (*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 roundworms and hookworms is as follows:

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

HEARTGARD® Plus is recommended for dogs 6 weeks of age and older.
For dogs over 100 lbs 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 minimizes the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD® Plus also provides effective treatment and control of roundworms (*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 roundworms (*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° - 25°C). Excursions between 59°F - 86°F (15° - 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 www.fda.gov/reportanimalae.

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 preventive 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 1, 6 and 12 chewables.

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

Approved by FDA under NADA # 140-971

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Rev. 05-2020

1050-1999-06.

US-PET-0199-2020-V3.

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

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Is prazosin the right drug for patients with recurrent urethral obstruction?

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These questions and more were addressed in the 2022 primary literature. Skim the highlights and start the new year on the cutting edge.

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QUIZ CORNER

QUIZ YOURSELF

on this issue's features

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1 **PROCEDURES PRO** **PAGE 15**

Which enucleation approach should be used when ocular neoplasia is suspected?

A. Transpalpebral
B. Subconjunctival

2 **TOP 5** **PAGE 25**

True or false? Gabapentin can be given as needed.

A. True
B. False

3 **A MATTER OF OPINION** **PAGE 30**

Which of the newly approved analgesic drugs for cats is labeled for chronic use?

A. Frunevetmab
B. Buprenorphine transdermal solution

4 **PATHOGEN PROFILE** **PAGE 55**

Extended spectrum beta-lactamase production in *Escherichia coli* confers resistance to which antibiotics?

A. Cephalosporins
B. Fluoroquinolones

5 **CASE ROUTES** **PAGE 59**

_____ is a first-line treatment for patients with acute hemorrhagic diarrhea syndrome.

A. Metronidazole
B. Ampicillin/sulbactam

Answer Key:
1: A 2: B 3: A 4: A 5: B

LOOK FOR THESE ARTICLES IN FUTURE ISSUES

- Surprises on Microscopic Fecal Examination
- High-Alert Medications
- Top 5 Zoonotic Disease Transmission Routes in Veterinary Medicine
- Anal Sac Abscess in a Chihuahua
- Application of a Modified Robert Jones Bandage
- Differential Diagnoses for Collapse

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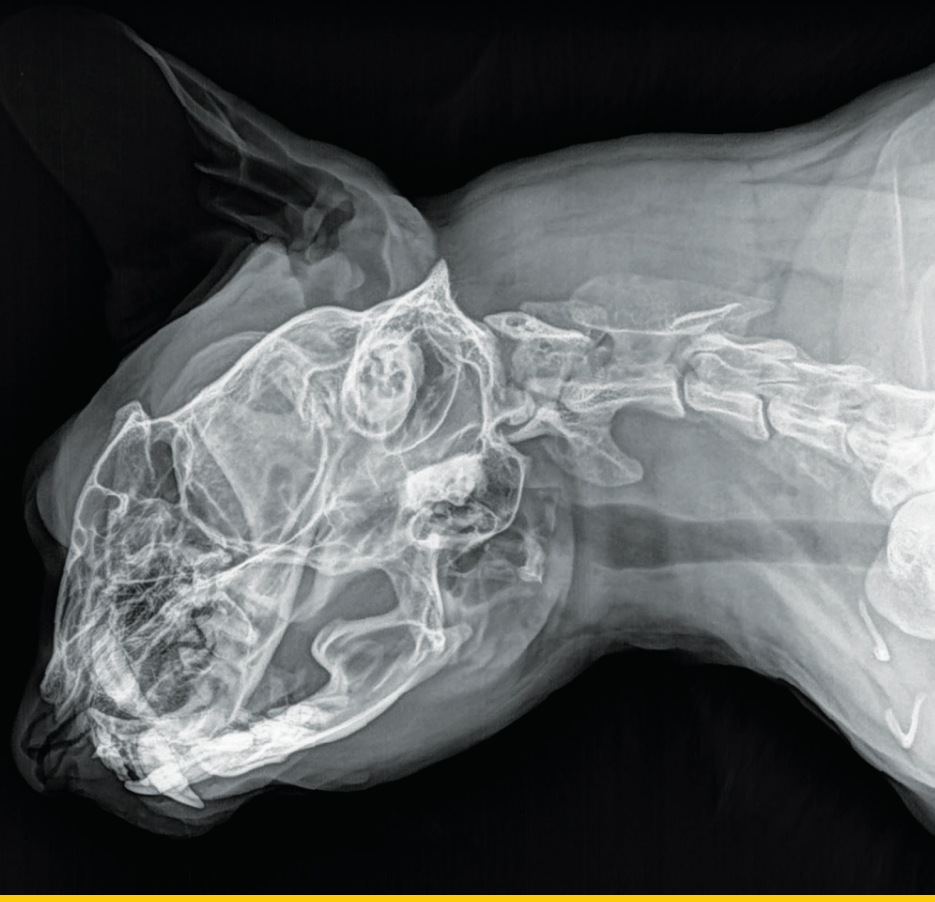

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Heartgard® Plus (ivermectin/pyrantel)

NexGard® (afoxolaner) Chewables

your trusted pair for protection

HEARTGARD® Plus (ivermectin/pyrantel) and *NexGard*® (afoxolaner) are designed with compliance in mind to keep your patients protected every month, year-round.

HEARTGARD® Plus and *NexGard*® are both formulated with the #1 tastes dogs prefer.[1,2]

Dog owners pairing **HEARTGARD Plus with *NexGard* were the most likely to purchase 12 months** of protection versus other common brand pairings in a 2020 assessment of parasiticide purchases in veterinary clinics.*[3]

Over **2 billion doses of HEARTGARD Plus**, and **over 270 million doses of *NexGard*** have been prescribed.[4,5]

Contact your Boehringer Ingelheim Representative to learn more.

IMPORTANT SAFETY INFORMATION: HEARTGARD Plus 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.

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, please see full prescribing information or visit www.NexGardClinic.com.

*Assessment was conducted by IDEXX® and leveraged veterinary clinic PIMS transaction level data for 2020. This analysis included veterinary practices with consistent data from 2018 to 2020. To be included, patients needed to have at least one parasiticide transaction in 2019 and 2020. The analysis was limited to loyal patients, where loyalty was defined as having one flea/tick control brand during the full three-year period.

1. Data on file at Boehringer Ingelheim. **2.** Data on file at Boehringer Ingelheim. **3.** Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA. **4.** Data on file at Boehringer Ingelheim. **5.** Data on file at Boehringer Ingelheim.

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See page 66 for product information summary.