

# Canine Pericardial Effusion

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## PROFILE

### Definition

- ▶ Pericardial effusion is a condition involving an accumulation of fluid within the pericardial sac.
  - Relatively uncommon
  - Diffuse regional distribution aside from coccidioidomycosis (infection with *Coccidioides immitis*), which is regional (southwestern United States)<sup>1</sup>

### Signalment

- ▶ Pericardial effusion occurs more commonly in large-breed dogs than smaller-breed dogs.<sup>2</sup>
  - Breeds at highest risk include golden retrievers, German shepherd dogs, brachycephalic breeds (eg, boxers, bulldogs, pugs), and cocker spaniels.<sup>2</sup>
- ▶ According to most studies, there is a male predilection.<sup>2,3</sup>

### Common Causes<sup>2</sup>

- ▶ Idiopathic or inflammatory
- ▶ Secondary to cardiac-associated tumors
  - Heart-base tumors (chemodectoma, ectopic thyroid carcinoma, other)
  - Hemangiosarcoma (mainly right atrial)
- ▶ Secondary to infiltrative or diffuse neoplasia
  - Mesothelioma
  - Lymphosarcoma
- ▶ Infectious
  - Coccidioidomycosis (regionally prevalent)
- ▶ See **Causes of Canine Pericardial Disease**, next page.

### Risk Factors

- ▶ Mesothelioma
  - Asbestos exposure has been linked to mesothelioma in humans; early pathology studies suggested a possible connection in dogs, but the link is unsubstantiated.<sup>5</sup>

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## CAUSES OF CANINE PERICARDIAL DISEASE

### Congenital Pericardial Disease

- ▶ Partial or total pericardial agenesis
- ▶ Pericardial cysts
- ▶ Peritoneopericardial diaphragmatic hernia

### Acquired Pericardial Disease/Effusion

#### Transudative effusions

- ▶ CHF-associated
- ▶ Hypoalbuminemia
- ▶ Uremia

#### Exudative effusions

- ▶ Septic pericarditis (bacterial, fungal, protozoal, algal)
- ▶ Uremia

#### Hemorrhagic effusions

- ▶ Coagulopathy
- ▶ Heart-base tumors
- ▶ Hemangiosarcoma
- ▶ Idiopathic pericardial effusion
- ▶ Left-atrial rupture (secondary to advanced valvular endocardiosis)
- ▶ Malignant mesothelioma
- ▶ Primary or metastatic pericardial neoplasia
- ▶ Trauma

### Pathophysiology

- ▶ Pericardial effusion, in the author's experience, is usually, but not always, associated with cardiac tamponade.
  - Cardiac tamponade occurs when pericardial pressures exceed right atrial pressures.
  - Acute cardiac tamponade is an acute fluid accumulation (blood) into the pericardium that causes a rapid increase in pericardial pressure with variable degrees of hemodynamic collapse.

CHF = congestive heart failure

PPDH = peritoneopericardial diaphragmatic hernia

RCHF = right-sided congestive heart failure

- The amount of fluid causing tamponade may be smaller in acute causes.
- Chronic cardiac tamponade results from slower accumulations of fluid, often as a result of infiltration and fibrosis of the pericardial sac that leads to decreased distensibility and, eventually, cardiac tamponade.
  - The slower development of pressure allows more pericardial stretch (often with large volumes of effusion) and time for the development of right-sided congestive heart failure (RCHF), ascites, and pleural effusion.

### History

- ▶ Patients with cardiac tamponade may present with: lethargy, inappetance, exercise intolerance, and acute collapse
  - Vomiting seems to be common.
- ▶ Abdominal distention and possibly dyspnea related to RCHF, which suggests a more chronic development of tamponade, may develop.

### Physical Examination

- ▶ Patients vary from bright and responsive to moribund.
- ▶ Mucous membrane color varies from pink to muddy or pale, often with delayed capillary refill time.
- ▶ Tachycardia and muffling of heart and/or lung sounds may be present.
- ▶ Arrhythmias may be present (ventricular arrhythmias are most common).
- ▶ Femoral pulses are generally weak; some patients exhibit pulsus alternans (varying strength of femoral pulses).
- ▶ Jugular distention generally present, with or without jugular pulsation.
- ▶ Dyspnea and muffled lung sounds may be present.
- ▶ An abdominal fluid wave may be detected.

### Clinical Signs

- ▶ Lethargy, inappetance, exercise intolerance
- ▶ Dyspnea, collapse

- ▶ Abdominal distention (not uniformly present)
- ▶ Vomiting

## DIAGNOSIS

### Definitive

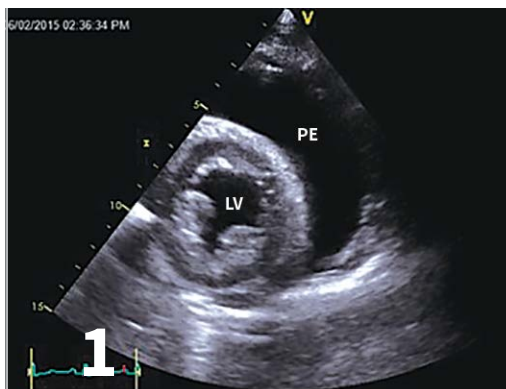
- ▶ Echocardiography confirms an echo-free space between the heart and the pericardium (**Figure 1**), may show cardiac tamponade (**Figure 2**), and may detect mass lesions.

### Differentials

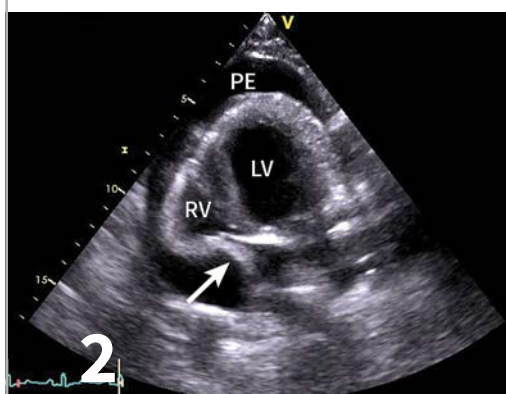
- ▶ Cardiac-associated hemangiosarcoma
- ▶ Infiltrative pericardial neoplasia
  - Mesothelioma
  - Carcinoma
  - Metastatic neoplasia
- ▶ Idiopathic pericardial effusion (or benign pericardial effusion)
- ▶ Heart-base tumors
  - Chemodectoma
  - Ectopic thyroid carcinoma
  - Other tumor type
- ▶ Peritoneopericardial diaphragmatic hernia (PPDH)
- ▶ Infectious pericarditis
  - Coccidioidomycosis (common in the southwest United States)
- ▶ Lymphosarcoma
- ▶ Coagulopathy (rodenticide, warfarin toxicity)
- ▶ Miscellaneous
  - Uremia-related (rare/theoretical)
  - Pancreatitis-related (rare/theoretical)
  - Congestive heart failure (CHF)-related (atypical for dogs); usually low-volume and unlikely to result in cardiac tamponade

### Laboratory Findings

- ▶ No findings are specific for pericardial effusion.
- ▶ Liver enzyme elevations associated with hepatic congestion may be present.
- ▶ Increased partial thromboplastin times or activated partial thromboplastin times are



- ▶ Right parasternal short-axis echocardiogram showing a large accumulation of pericardial effusion. (PE = pericardial effusion, LV = left ventricle)

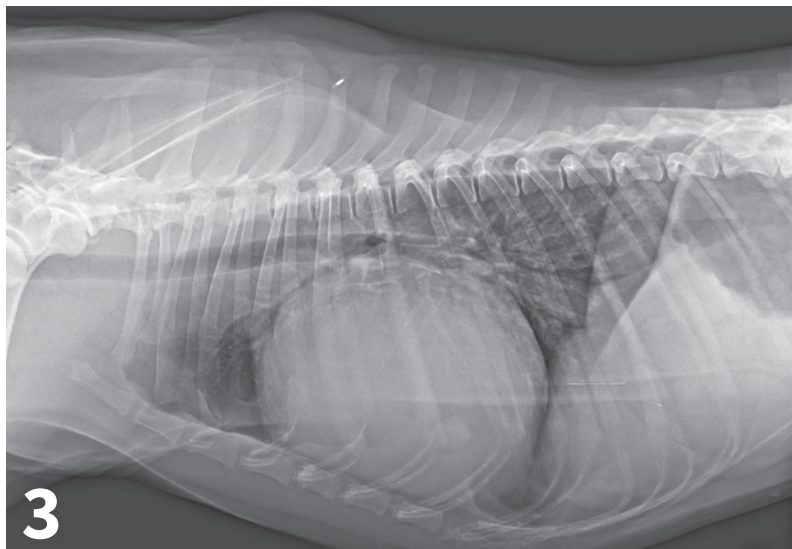


- ▶ Four-chamber left apical echocardiographic view showing moderate pericardial effusion with cardiac tamponade. Arrow shows diastolic collapse of the right atrium consistent with cardiac tamponade. (PE = pericardial effusion, LV = left ventricle, RV = right ventricle)

found in patients with coagulopathy.

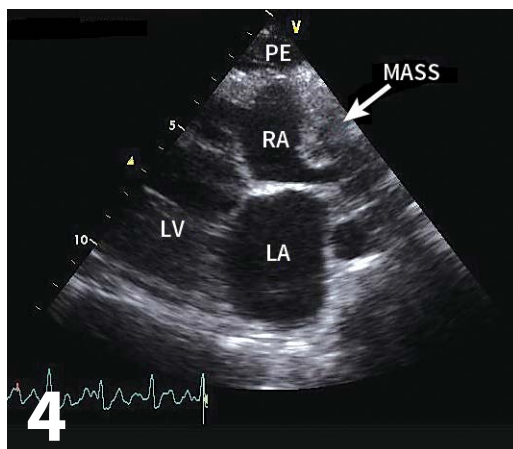
- ▶ Pericardial fluid analysis
  - In the author's clinical experience, most fluid samples of the pericardial effusions are hemorrhagic (and as such, rarely diagnostic).
  - Serous effusion may be associated with secondary processes based on the author's clinical experience.

**Liver enzyme elevations associated with hepatic congestion may be present.**



▲ Right lateral thoracic radiograph for patient presenting with acute collapse. The heart is globoid while the pulmonary vasculature is small. The caudal vena cava is hard to visualize but would likely be dilated.

▶ Right parasternal long-axis echocardiographic view of a dog with a small accumulation of pericardial effusion and an infiltrative right atrial mass (hemangiosarcoma most likely). (PE = pericardial effusion, RA = right atrium, LA = left atrium, LV = left ventricle)



- Serosanguinous effusion not consistent with hemangiosarcoma can be seen with mesothelioma, idiopathic pericarditis, or heart-base tumors.
  - Attempts to use pericardial fluid pH to effectively predict the cause have not been reliable.<sup>4</sup>
- Serum troponin levels: in 1 study, patients with right atrial hemangiosarcoma had higher levels of serum troponin (>0.25 mg/

dL) than patients with noncardiac hemangiosarcoma and other causes of pericardial effusion.<sup>6</sup>

–This test may provide additional insight in cases of idiopathic pericardial effusion.<sup>6</sup>

- Mesothelioma is a difficult cytologic diagnosis given that activated mesothelial cells develop as a result of other types of pericardial disease and can appear atypical when not neoplastic.

### Imaging

#### ▶ Thoracic radiography

- The heart may be relatively normal (acute hemorrhage) or globoid (chronic effusion; **Figure 3**). Distention of the caudal vena cava, ± pleural effusion, ± peritoneal effusion, may also be present.
- Cardiac-associated tumors may be suspected based on atypical cardiac silhouette.
- Metastatic lesions may be present (most commonly with cardiac hemangiosarcoma).
- When PPDH is suspected, overlap of peritoneum and pericardium will be noted; abdominal viscera may be seen within the pericardium.
  - PPDH is frequently associated with sternal deformities.

#### ▶ Echocardiography

- Survey of the heart base and heart for cardiac-associated tumors.
  - Right atrial masses are most typically hemangiosarcoma (**Figure 4**).<sup>7</sup>
  - Heart-base tumors directly adjacent to the base of the aorta may be chemodectoma, ectopic thyroid carcinoma, or other tumors, including hemangiosarcoma.<sup>7</sup>
  - Echocardiography by an experienced operator is very specific (>99%) with variable sensitivity (74%–82%) depending on the cause.<sup>7</sup>
  - Serial echocardiography increases the sensitivity of echocardiography.
- Evaluate for the presence of cardiac tam-

CHF = congestive heart failure  
 RCHF = right-sided congestive heart failure  
 PPDH = peritoneopericardial diaphragmatic hernia

ponade (eg, diastolic collapse of the right atrium) (**Figure 2**, page 67).

- Evaluate the thickness of the pericardium.
- When finding is echo-negative for tumor, the main differential diagnosis is primary pericardial disease (eg, idiopathic pericarditis, mesothelioma) or occult right atrial mass (right auricular masses are not always easy to visualize).
- In cases of echo-positive for tumor, small (2-3 cm), well-circumscribed masses adjacent to the aorta are more consistent with chemodectoma. Right heart-associated masses, often irregular, are more typically hemangiosarcoma, but neuroendocrine tumors (eg, thyroid carcinoma, chemodectoma) have been described in this region as well.<sup>7</sup>
- PPDH: tissue within the pericardium (most typically omental fat, hepatic tissue).
- ▶ Specialized testing
  - Transesophageal echocardiography may allow visualization of additional occult mass lesions but requires general anesthesia and specialized equipment and is technically challenging.
  - CT and MRI may reveal additional cardiac-associated tumors but require general anesthesia, significant expense, and specialized equipment.

### Postmortem Findings

- ▶ Hemangiosarcoma with hemopericardium may have pulmonary metastatic lesions and/or splenic hemangiosarcoma.
  - Pericardial tissue is usually normal.
- ▶ Hemopericardium is evident in heart-base tumors. Pericardial tissue may be slightly fibrotic (chronic fluid accumulation) or may be normal.
- ▶ Primary pericardial disease
  - Mesothelioma: Thickening, nodular infiltration of parietal and/or visceral pericardium with neoplastic mesothelial cells. Neoplasia may extend to the pleural space.

- Idiopathic pericardial effusion (ie, fibrosing pericarditis): Varying degree of fibrosis and inflammatory infiltrate.
  - Pericardium is thickened and nonelastic.
  - There is no evidence of neoplasia.

### TREATMENT

#### Pericardiocentesis (In-Patient Preferred)

- ▶ Performed as follows:
  - Place IV catheter.
  - Lightly sedate the patient if required.
  - Administer local anesthesia (2% lidocaine infused at the predicted centesis site).
  - Position patient in left lateral or sternal recumbency.
  - Aseptically prepare the site.
    - The preferred location is the fifth right intercostal space, just below the costochondral junction (at the cardiac notch in the lungs), or as best defined by cardiac ultrasound.

## Hemangiosarcoma with hemopericardium may have pulmonary metastatic lesions and/or splenic hemangiosarcoma.

- Echocardiographic guidance is optional in most cases but recommended in patients with a low-volume effusion.
- For this procedure, a 19-gauge (17-gauge placement needle) or 16-gauge (14-gauge placement needle) through-the-needle catheter is the author's preferred tool.
  - For the emergency, 14- or 16-gauge, 6-inch, over-the-needle catheters with additional side holes are frequently used

but are more likely to result in incomplete tap or spillage of the effusion into the thorax.

- With electrocardiography (ECG) monitoring, advance the needle into the pericardial sac.
  - There is typically a blood flash-back.
  - Thread the catheter through the needle.
  - Once fully threaded, retract the needle from the chest and place the needle guard according to the manufacturer's instructions.
- Aggressive ventricular arrhythmias generally suggest contact with the heart; pull back slightly if necessary.
- Set aside a fluid sample to observe for clotting.
  - Clotted blood indicates cardiac or vessel puncture and necessitates needle retraction.
- Continue to monitor the ECG throughout the pericardiocentesis.
- Collect samples for fluid analysis (EDTA tube, serum tube).
- Look for decrease in heart rate, which is consistent with relief of the cardiac tamponade.

ECG = echocardiogram  
MST = mean survival time  
PPDH = peritoneopericardial diaphragmatic hernia

## WHAT ABOUT CATS?

- Primary pericardial disease is rare in cats.<sup>8</sup>
- Pericardial effusion as a manifestation of left-sided heart failure in cats is the most common cause (75% of cases).<sup>8</sup> It generally responds to diuretic therapy and does not result in cardiac tamponade.
- Lymphosarcoma and mesothelioma are the most common cardiac neoplasms in cats.<sup>8</sup>
- Idiopathic pericardial effusion occurs rarely in cats and involves a large accumulation of a pure transudate; it is often recurrent.
- PPDH is more common in cats than dogs and is often an incidental finding.<sup>8</sup>
- Pericardiocentesis is easy to perform on cats using a 23- or 25-gauge butterfly set. Location is optimized using echocardiographic guidance.

- Fluid administration may be required depending on patient's hemodynamic status.
- Following the procedure, ideally monitor the ECG for 12 to 24 hours for arrhythmias and for increasing heart rate consistent with possible recurrent cardiac tamponade.

## Medical

- Rarely effective
- Anti-inflammatory therapy may be used to avoid fluid recurrence.
  - Based on the author's clinical experience, metronomic nonsteroidal anti-inflammatory drug therapy may be used for patients with mesothelioma.
  - Prednisone in anti-inflammatory doses may be used to treat idiopathic effusions (extrapolated from human practice).
- Chemotherapy can be used for neoplastic causes.
  - Adriamycin may be given for therapy with hemangiosarcoma.<sup>9</sup>
  - Toceranib (Palladia, zoetisus.com) therapy is used by oncologists for patients with heart-base masses and hemangiosarcoma in the author's experience.
  - Aminocaproic acid (Amicar, amicar.org) may be prescribed for large-breed dogs to reduce tumor bleeding (extrapolation from human medicine).

## Surgical

- Most commonly performed by specialists
- Thoracotomy for subtotal pericardiectomy is the best approach for restrictive pericardial disease or if owners choose to be aggressive with tumor biopsy or resection (right auricular hemangiosarcoma lesions).
- Thoracoscopy is used for minimally invasive exploration of the thorax to make a pericardial window.
  - It is palliative for heart-base masses and hemangiosarcoma (no further episodes

of cardiac tamponade); it is potentially curative for idiopathic pericarditis.

#### CLIENT EDUCATION

- ▶ Pericardial effusion almost always returns unless a pericardial window is made; how and when it returns helps establish likely diagnosis in tumor-negative dogs.
  - Acute, rapid return is most consistent with acute hemopericardium related to hemangiosarcoma.
  - Slow, gradual accumulation is more typical with primary pericardial disease (eg, idiopathic, mesothelioma) or a heart-base tumor.
- ▶ Echocardiogram-negative dogs with first-time pericardial effusion should have pericardiocentesis without additional therapy to avoid spread of pericardial mesothelioma to the pleural space.
- ▶ In the author's experience, a substantial percentage of patients diagnosed with idiopathic pericarditis will experience future pleural effusion and subsequent diagnosis of mesothelioma (postpericardectomy or pericardial window). Therefore, this remains on the differential diagnosis list for a minimum of 6 months.
- ▶ Anecdotal evidence suggests that Yunnan Baiyao is an herbal remedy that may decrease tumor bleeding.

#### FOLLOW-UP

- ▶ Instruct owners to monitor for signs of recurrent cardiac tamponade.
- ▶ Perform a recheck echocardiogram 2 weeks post-discharge and periodically thereafter as the client wishes or can afford.

#### IN GENERAL

##### Relative Cost

- ▶ \$\$\$\$-\$\$\$\$\$

#### COST KEY

\$ = up to \$100  
\$\$ = \$101–\$250  
\$\$\$ = \$251–\$500  
\$\$\$\$ = \$501–\$1000  
\$\$\$\$\$ = more than \$1000

#### Prognosis

- ▶ Cardiac tamponade is a medical emergency and is occasionally fatal.
- ▶ Neoplastic causes associated with variable long-term prognosis.
  - Patients with cardiac hemangiosarcoma have the poorest prognosis (mean survival time [MST] ranges from 16 days without treatment, 46 days with pericardiectomy and tumor resection, 164 days with pericardiectomy, tumor resection and chemotherapy).<sup>3,9</sup>
  - Patients with chemodectoma have a more favorable prognosis but generally experience recurrent effusion.
  - Overall survival data are less clear because biopsy diagnosis is less commonly made premortem.
  - In 1 study, ( $n = 24$ ) dogs with biopsy-confirmed heart-base masses having pericardiectomy had significantly longer survival (MST = 730 days, 14 dogs with pericardiectomy vs 42 days, 10 dogs without pericardiectomy), regardless of whether they had pericardial effusion at the time of surgery.<sup>5</sup>
  - Malignant mesothelioma may be slow and insidious, but patients ultimately develop malignant pleural effusion.
    - MST is difficult to predict for this disease as diagnosis can be elusive; in 1 study MST was 13.6 months.<sup>7</sup>
  - Lymphosarcoma generally responds well to treatment for the systemic disease.<sup>10</sup>
- ▶ Idiopathic pericarditis
  - Patients generally do well, but most require pericardiectomy or pericardial

**Pericardial effusion almost always returns unless a pericardial window is made; how and when it returns helps establish likely diagnosis in tumor-negative dogs.**

window. (MST = 15.3 months).<sup>3</sup>

- In the author's clinical experience, a significant percentage of dogs with idiopathic pericarditis are ultimately diagnosed with mesothelioma.
- One study suggested significantly better survival after thoracotomy with subtotal pericardiectomy than thorascopic pericardial window,<sup>11</sup> although this is still controversial. ■■■

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## Suggested Reading

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# NexGard® (afoxolaner) Chewables

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

### Description:

NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables 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). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5-[3-chloro-2-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl].

### Indications:

NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of Black-legged tick (*Ixodes scapularis*), American Dog tick (*Dermacentor variabilis*), Lone Star tick (*Amblyomma americanum*), and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

### Dosage and Administration:

NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

### Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs	28.3	One
24.1 to 60.0 lbs	69	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NexGard can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

### Flea Treatment and Prevention:

Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard 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 control product.

### Tick Treatment and Control:

Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

### Contraindications:

There are no known contraindications for the use of NexGard.

### 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.

### Precautions:

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

### 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. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

**Table 1: Dogs With Adverse Reactions.**

	Treatment Group			
	Afoxolaner		Oral active control	
	N <sup>1</sup>	% (n=415)	N <sup>2</sup>	% (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

<sup>1</sup>Number of dogs in the afoxolaner treatment group with the identified abnormality.

<sup>2</sup>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.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or [www.merial.com/NexGard](http://www.merial.com/NexGard). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

### Mode of Action:

Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitability results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

### Effectiveness:

In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively. Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*, 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days.

### 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 (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistry, 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, NexGard was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

### Storage Information:

Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

### How Supplied:

NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 69 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

NADA 141-406, Approved by FDA  
Marketed by: Frontline Vet Labs™, a Division of Merial, Inc.  
Duluth, GA 30096-4640 USA

Made in Brazil.

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