Date of Approval: December 19, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-273

Vetmedin®

(pimobendan)

Chewable Tablets

Dogs

This supplement provides for the addition of the indication for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease. Stage B2 preclinical myxomatous mitral valve disease (MMVD) refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.

Sponsored by:

Boehringer Ingelheim Animal Health USA, Inc.

Executive Summary

Vetmedin® (pimobendan) is approved for the delay of onset of congestive heart failure (CHF) in dogs with Stage B2 preclinical myxomatous mitral valve disease (MMVD). Stage B2 preclinical MMVD refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral valve regurgitation and cardiomegaly. MMVD should be diagnosed based on comprehensive physical and cardiac examinations, which should include radiography and echocardiography. The most recent (2019) consensus statement of the American College of Veterinary Internal Medicine (ACVIM) on degenerative or chronic valvular heart disease in dogs uses the term MMVD when describing acquired heart disease that is specific to the mitral valve.[1]

This supplemental approval adds a new indication to the existing fully approved Vetmedin® under NADA 141-273. Vetmedin® was previously approved for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to clinical MMVD or dilated cardiomyopathy (DCM), for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

Pimobendan is an inodilator, meaning it combines the properties of a positive inotropic agent with those of a peripheral vasodilator. By increasing myocardial contractility and dilating peripheral blood vessels, the drug reduces cardiac afterload. Pimobendan exerts its stimulatory myocardial effect by a dual mechanism of action: it increases the calcium sensitivity of cardiac myofilaments and inhibits phosphodiesterase III. The vasodilation is a result of the drug's inhibitory effect on phosphodiesterase III.

Safety and Effectiveness

The approval of this new indication is supported by substantial evidence of effectiveness from two multi-site field studies, which together demonstrated that Vetmedin® is effective. The first study is a multi-center field study known as the Evaluation of Pimobendan In dogs with Cardiomegaly (EPIC) study (No. 2009045). This randomized, vehicle-controlled study was designed to evaluate if chronic oral administration of Vetmedin® could delay the onset of CHF in dogs with Stage B2 preclinical MMVD. The study enrolled 363 client-owned dogs, with an effectiveness population of 353 dogs (178 treated with Vetmedin® and 175 with a vehicle control). The primary endpoint was a composite of the development of left-sided CHF, euthanasia for a cardiac reason, or death presumed to be cardiac in origin. An interim analysis of the data provided such strong evidence of effectiveness that the study was terminated early. The final analysis confirmed these findings, showing a statistically significant difference between the groups. The median time to the primary endpoint for dogs in the Vetmedin® group was 1,127 days, compared to 732 days for the control group. This represents a clinically significant delay of 395 days, or approximately 13.2 months, in the onset of congestive heart failure.

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[1] Keene, B., et al. (2019) ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *J Vet Intern Med*. 33(3):1127-1540.

The second study (No. 2019035) was a multi-site, single-arm field study that used a historical control group derived from the EPIC study. This trial was designed to further support the effectiveness of Vetmedin® in a subset of dogs with Stage B2 preclinical MMVD, defined by a left atrial-to-aortic root ratio (LA/Ao) of 1.8 or greater. The study enrolled 161 client-owned dogs, with an effectiveness population of 125 dogs, all of whom received Vetmedin®. The primary endpoint was treatment success at 365 days, defined as the absence of radiographic evidence of CHF and no significant progression of clinical signs requiring additional therapy. The results showed an estimated treatment success rate of 79.2%. Of the 125 dogs, 99 successfully completed the study without disease progression, while 26 were classified as treatment failures due to developing CHF, cardiac-related death, or other advancing clinical signs. The study's success criteria were met, as the lower bound of the 95% confidence interval for the success rate (70.3%) was well above the pre-specified threshold of 54%.

The safety of Vetmedin® in dogs is supported by the target animal safety study conducted for the original approval of NADA 141-273. The safety profile of Vetmedin® in dogs with Stage B2 MMVD was evaluated in the two field studies. In the EPIC study, adverse reactions were observed in both the treatment and control groups, with many findings being consistent with the natural progression of MMVD and comorbidities common in older dogs. The most frequently reported adverse reaction was cough, with a similar incidence in both the Vetmedin® group (21.4%) and the control group (23.2%). Other non-cardiac adverse reactions in the Vetmedin® group included musculoskeletal pain (10.4%), diarrhea (10.4%), and vomiting (9.9%). In the second study (No. 2019035), the most common adverse reactions reported in the 161 dogs treated with Vetmedin® were gastrointestinal, including vomiting (36.6%) and diarrhea (32.9%), followed by cough (29.8%).

Conclusions

Based on the data submitted for this supplemental approval, the Food and Drug Administration (FDA) determined that Vetmedin® is safe and effective when used according to the labeling for the delay of onset of CHF in dogs with Stage B2 preclinical MMVD. This supplemental approval qualifies for three years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) because the supplemental application included effectiveness studies.

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I. GENERAL INFORMATION

A. File Number

NADA 141-273

B. Sponsor

Boehringer Ingelheim Animal Health USA, Inc.
3239 Satellite Blvd.
Duluth, GA 30096

Drug Labeler Code: 000010

C. Proprietary Name

Vetmedin®

D. Drug Product Established Name

pimobendan

E. Pharmacological Category

Inodilator (calcium sensitizer and phosphodiesterase III inhibitor)

F. Dosage Form

Chewable Tablets

G. Amount of Active Ingredient

1.25, 2.5, 5, and 10 mg pimobendan per tablet

H. How Supplied

Tablets are packaged in bottles containing 50 tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Vetmedin® (pimobendan) should be administered orally at a total daily dose of 0.23 mg/lb (0.5 mg/kg) body weight, using a suitable combination of whole or half tablets. The total daily dose should be divided into 2 portions that are not necessarily equal, and the portions should be administered approximately 12 hours apart (i.e., morning and evening). The tablets are scored, and the calculated dosage should be provided to the nearest half tablet increment.

K. Route of Administration

Oral

L. Species

Dogs

M. Indications

Vetmedin® (pimobendan) is indicated for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease. Stage B2 preclinical myxomatous mitral valve disease (MMVD) refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.

Vetmedin® (pimobendan) is indicated for the management of the signs of mild, moderate, or severe congestive heart failure (CHF) in dogs due to clinical MMVD or dilated cardiomyopathy (DCM). Vetmedin® is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

N. Effect of Supplement

This supplement provides for the addition of the indication for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease. Stage B2 preclinical myxomatous mitral valve disease (MMVD) refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved Vetmedin® total daily dose of 0.23 mg/lb (0.5 mg/kg) divided into 2 portions administered approximately 12 hours apart. The FOI Summary for the original approval of NADA 141-273 dated April 30, 2007, contains dosage characterization information for dogs.

B. Substantial Evidence

The effectiveness of Vetmedin® for the delay of onset of congestive heart failure (CHF) in dogs with Stage B2 preclinical MMVD is based on results from two multi-site field studies. These studies demonstrated that Vetmedin® is effective and has an adequate safety profile in the target population. Stage B2 preclinical MMVD refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.[2]

Study No. 2009045 was conducted in dogs with ACVIM Stage B2 preclinical MMVD. The study did not meet certain characteristics of an adequate and well-controlled study [21 CFR 514.117]. This study was considered corroborative to support this indication when evaluated in conjunction with Study No. 2019035, a single-arm field

[2] Keene, B., et al. (2019) ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *J Vet Intern Med*. 33(3):1127-1540.

study with a historical control that enrolled a subset of dogs with more advanced ACVIM Stage B2 preclinical MMVD (dogs with a left LA/Ao ratio ≥1.8). All enrolled dogs were treated with Vetmedin® and the effectiveness of Vetmedin® was compared to a subset of the control group enrolled in Study No. 2009045 that met the enrollment criteria for Study No. 2019035.

These two studies, when considered together, demonstrate the effectiveness of Vetmedin® for the delay of onset of CHF in dogs with Stage B2 preclinical MMVD.

1. Multi-Site Field Study

   Title: Evaluation of Pimobendan in Dogs with Cardiomegaly Caused by Preclinical Mitral Valve Disease – EPIC. (Study No. 2009045)

   Study Dates: August 2010 to November 2016

   Study Locations:

United States	International
Columbus, OH	Moorabbin, Australia
Blacksburg, VA	Guelph, Ontario, Canada
Overland Park, KS	Meaux, France
Gilbert, AZ	Villars Les Dombes, France
Los Angeles, CA	Munich, Germany
New York, NY	Duisburg, Germany
College Station, TX	Wiesloch, Germany
Raleigh, NC	Samarate, Italy
Ithaca, NY	Danderyd, Sweden
Englewood, CO	Kanagawa, Japan
Chicago, IL	Utrecht, Netherlands
Rohnert Park, CA	Murcia, Spain
Gainesville, FL	Uppsala, Sweden
Philadelphia, PA	Hatfield, Herts, United Kingdom
Towson, MD	Gloucestershire, United Kingdom
North Grafton, MA	Etwall, Derby, United Kingdom
Tampa, FL	
Madison, WI	

   Study Design:

   Objective: The study objective was to determine whether chronic oral administration of pimobendan (Vetmedin®), in dogs with evidence of increased heart size secondary to Stage B2 preclinical MMVD, could delay the onset of signs of CHF.

   Study Animals: A total of 363 client-owned dogs were enrolled in the study; 40.2% of the dogs were female (intact and spayed) and 59.8% were male (intact and neutered). The effectiveness population consisted of 353 dogs of various breeds. Cavalier King Charles Spaniels were the most common breed, accounting for 45.6% of the effectiveness population, with 12.7% mixed breed dogs, 3.7% dachshunds, 2.3% poodles, 2.3% Yorkshire terriers, and 27.5% other

breeds. Body weights ranged from 4.1 to 15.0 kg (enrollment limited to dogs weighing 15 kgs or less) and age ranged from 6 to 17 years. All dogs were examined for evidence of Stage B2 preclinical MMVD prior to enrollment.

Experimental Design: This multi-center field study was conducted in accordance with Good Clinical Practice (GCP) guidelines. Client-owned dogs diagnosed with Stage B2 MMVD were enrolled and randomized in a 1:1 ratio to receive either Vetmedin® or a vehicle control chewable tablet.

Table II.1. Treatment Groups

Treatment Group	Dose	Safety Population	Effectiveness Population
Vetmedin® (pimobendan)	0.5 mg/kg/day	182	178
Control (vehicle)	0 mg/kg/day	181	175

Drug Administration: Of the 363 dogs enrolled in the study, 182 received Vetmedin® 2.5 mg tablets at a target dose of 0.5 mg/kg per day. The median dose administered to dogs in the Vetmedin® group was 0.49 mg/kg per day, with a range from 0.34 mg/kg to 0.68 mg/kg. A total of 181 dogs received the vehicle control product, which was visually identical to the Vetmedin® 2.5 mg tablet and contained only inactive ingredients. The calculated daily dose for each group was divided into two administrations, adjusted to whole and half tablets, approximately 12 hours apart. Dogs in both treatment groups were dosed according to Table II.2. The dose of study medication was not adjusted throughout the study.

Table II.2. Daily Dosing Chart (Vetmedin® or Control)

Body Weight (kg)	First dose: Number of 2.5 mg tablets (morning)	Second dose: Number of 2.5 mg tablets (evening)
4.1-6.9	0.5	0.5
7.0-8.9	0.5	1
9.0-12.9	1	1
13.0-15.0	1.5	1.5

Measurements and Observations: Dogs were eligible for inclusion if the following Stage B2 preclinical MMVD criteria were met:

- Moderate to high intensity systolic heart murmur (grade ≥3/6)
- Echocardiographic evidence of MMVD defined as valvular lesions (leaflet thickening, valve prolapse, ruptured chordae tendineae)
- Presence of mitral regurgitation on Doppler echocardiogram
- Echocardiographic evidence of left atrial dilatation (LA/Ao ratio ≥1.6)
- Increased left ventricular internal-diastolic diameter, normalized for body weight (LVIDDN ≥1.7)

- Radiographic evidence of cardiomegaly, measured by vertebral heart size (VHS >10.5)

Murmur grading was completed with the dog standing on all four limbs during auscultation. Intensity of heart murmurs was graded on a scale of 1 to 6:

Table II.3. Heart Murmur Grading

Grade	Description
1	A low intensity murmur heard in a quiet environment only after careful auscultation over a localized cardiac area.
2	A low intensity murmur heard immediately when the stethoscope was placed over the point of maximal intensity.
3	A murmur of moderate intensity.
4	A high intensity murmur that was auscultated over several areas without any palpable precordial thrill.
5	A high intensity murmur with a precordial thrill.
6	A high intensity murmur with a palpable thrill that may have been heard when the stethoscope is slightly lifted off the chest wall.

For echocardiography measurements, a standard echocardiogram was performed with dogs unsedated and placed in right lateral recumbency. Right parasternal views (long and short axis) were used to measure heart dimensions and evaluate cardiac structures (including valves).

Left atrial enlargement was assessed by measuring the LA/Ao ratio. The Ao was measured with the first caliper placed at the midpoint of the convex curvature of the wall of the right aortic sinus. The caliper cross was positioned as close as possible to the blood-tissue interface. The second caliper was positioned at the point where the aortic wall and the non-coronary and left coronary aortic cusps merged. The LA was measured by extending the Ao line to the blood-tissue interface of the LA wall. The measurement was done in early ventricular diastole using the first frame after aortic ejection where the Ao appeared as a symmetric three-leaf clover with closed aortic valves and a teardrop shaped LA.

Ventricular enlargement was calculated using the left ventricular internal diameter in diastole (LVIDd) measured via M-mode from the right parasternal short axis view at the level of the papillary muscles. LVIDDN was calculated (by echocardiograph instrumentation or by hand) via the following formula:

$$LVIDDN = \frac{LVIDd}{[BW \times 0.45359]0.294}$$

LVIDDN = Normalized left ventricular internal-diastolic diameter
LVIDd = Left ventricular internal diameter in diastole (measured in centimeters)
BW = Body weight (measured in pounds)

Investigators measured VHS via radiograph by transforming the cardiac long and short axes from caliper measurement values into whole and 0.1 increments of VHS units. Observers compared the measurements of each axis to the vertebral silhouettes and measured the length of each axis (in vertebrae to the nearest 0.1

VHS unit) from the cranio-ventral margin of T4 caudally. The two VHS measurements (for long and short axis) were summed to produce the total VHS.

Dogs were excluded from the study if found to have: current or previous evidence of cardiogenic pulmonary edema, clinically significant tachyarrhythmias, cardiac disease other than MMVD, known significant systemic or other organ related disease that would have limited the dog's life expectancy, evidence of pulmonary hypertension (right atrium to right ventricle gradient > 65 mmHg), were pregnant or lactating female dogs, or were pretreated with prohibited concomitant medications (Table II.4) for 14 or more consecutive days. If prohibited concomitant medications were administered prior to enrollment but for less than 14 consecutive days, a washout period of 30 days before Day 0 was required.

Table II.4. Prohibited Concomitant Medications

Prohibited Concomitant Medications
ACE-inhibitors
Angiotensin II receptor blockers
Antiarrhythmics
Anticholinergics
Beta-blockers
Diuretics
Inodilators
Phosphodiesterase V inhibitors
Positive inotropes
Pressor agents
Vasodilators (including nitric oxide donors)
Other: iloprost, epoprostenol, bosentan, and known cardiac toxins e.g., adriamycin

Before inclusion on Day 0, a case history was taken for each dog. A physical examination, hematology and blood chemistry evaluations, and other examinations of cardiac function, including thoracic radiographs and echocardiography, were performed. Dogs began study treatment on Day 0.

Physical and cardiac examinations were also conducted at Day 35 ± 7, and approximately every 4 months after Day 0.

The primary endpoint was a composite of the development of left-sided CHF, or euthanasia for a cardiac disease related reason, or death presumed to be cardiac in origin. A dog was considered to have left-sided CHF when there was radiographic evidence of cardiogenic pulmonary edema as indicated by an interstitial or alveolar pattern in conjunction with left sided cardiomegaly. In addition to these radiographic findings, the dog must also have been showing contemporaneous clinical signs consistent with left-sided congestive heart failure including increased respiratory effort and rate (by comparison to previously noted values for this patient). If a dog died in the absence of evidence of a non-cardiac cause of death (if possible, confirmed by post-mortem examination), prior to radiographic confirmation of pulmonary edema, it was also considered to have reached the primary endpoint.

Each case of CHF was verified by an endpoint committee, under masked conditions, based on the radiographs alone. The endpoint committee for a case included three investigators from the study. The endpoint confirmation was evaluated by two investigators with disagreements adjudicated by a third investigator. No investigator reviewed cases from their own site. Only if the endpoint committee verified CHF was the dog considered to have reached the primary endpoint.

Secondary variables included overall survival time (all-cause mortality) and the effect of Vetmedin® on the heart size on Day 35 ± 7 days compared to baseline.

Study Duration: The study duration was 4 years and 4 months. The study was planned to have a 2-year recruitment phase with up to 3 additional years to follow disease progression. The study design included an interim analysis which allowed the study to be terminated early due to evidence of effectiveness or concerns about safety. The interim analysis committee consisted of three non-sponsor, non-study affiliated experts. The interim analysis was conducted in January 2015, about 4 years after first subject enrollment. Based on evidence of effectiveness from the interim analysis, the study was terminated in March 2015.

Statistical Methods:

Analysis Populations: The safety population consisted of 363 dogs (Vetmedin® n = 182; control n = 181) that were randomized and received at least 1 dose of study medication. The effectiveness population consisted of 353 dogs (Vetmedin® n = 178; control n = 175) from the safety population which did not have major violations to the inclusion and exclusion criteria.

The experimental unit was the individual animal. The primary variable for effectiveness was the time interval from first treatment to reaching the primary endpoint. Dogs that did not reach the primary endpoint were censored with days on study until the dogs left the study, or until study termination. For the primary variable, Kaplan-Meier analysis was used to construct the survival curves for the two treatment groups. The median time-to-event and its 95% confidence intervals were reported. The log-rank test was used for comparison of survival curves between the two groups. The primary variable was also analyzed using a Cox Proportional Hazard model with treatment group as a fixed effect, the hazard ratio and its 95% confidence interval were reported.

The study protocol pre-specified an interim analysis which allowed the study to be terminated early due to evidence of effectiveness or concerns about safety. The O'Brien-Fleming alpha spending function was used for the control of Type I error probability, with the nominal alpha level (two-sided) of 0.0244 to be spent at the interim analysis, and 0.0429 at the final analysis.

Results:

Interim analysis: The interim analysis was conducted in January 2015 on data collected up to October 2014, with 354 animals included in the effectiveness analysis. The p-value of the log-rank test on the comparison of the time to the primary endpoint between the two treatment groups was 0.0097, with a hazard

ratio of 0.6558 (95% confidence interval 0.4751 to 0.9051) estimated from the Cox model in favor of the Vetmedin® group. The p-value for treatment comparison was less than the nominal alpha level of 0.0244 per O'Brian-Fleming alpha spending function; therefore, the criterion for study termination due to evidence of effectiveness was met at the interim analysis. The members of the interim analysis committee recommended terminating the study for proven effectiveness. The study was terminated in March 2015.

Final analysis: A final analysis was conducted using all the data collected up to March 2015. Of the 343 dogs included in the effectiveness population in the final analysis, 73 of 173 dogs in the Vetmedin® group and 91 of 170 dogs in the control group reached the primary endpoint. There were 57 cases with verified CHF and 16 cases of death or euthanasia for cardiac disease related reason in the Vetmedin® group, and 77 cases with verified CHF and 14 cases of death or euthanasia for cardiac disease related reason in the control group.

In the final analysis, the log-rank test for the comparison of the Kaplan-Meier curves between the two treatment groups had a p-value of 0.0008. The median (95% confidence interval) time to the primary endpoint was 1,127 (847, high end not estimable) days in the Vetmedin® group, and 732 (616 to 849) days in the control group. This translates to a difference of 395 days (13.2 months) in the median time to the primary endpoint in favor of the Vetmedin® group. The hazard ratio (95% confidence interval) from the Cox Proportional hazard model was 0.591 (0.434 to 0.805).

The time to onset of verified CHF was evaluated as a component of the primary endpoint separately. The median time to onset of CHF was 1,231 days in Vetmedin® group versus 806 days in the control group. Thus, administration of Vetmedin® to dogs with Stage B2 preclinical MMVD resulted in the prolongation of the time to onset of verified CHF by 425 days (14.2 months), compared to dogs receiving vehicle control product.

The p-value from the log rank test was smaller than the pre-specified nominal alpha level of 0.04287 for the final analysis; therefore, the difference between the Vetmedin® and the control groups in the time to the primary endpoint was considered to be statistically significant.

Secondary variables: All-cause mortality and heart size reduction were analyzed. Time-to-event analysis for all-cause mortality showed a prolonged survival for dogs in the Vetmedin® group. The median survival time was 1,015 days in the Vetmedin® group compared to 878 days in the control group. Analysis of heart size on Day 35 ± 7 compared to baseline demonstrated a decreased LVIDDN (measurement of left ventricular enlargement) in the Vetmedin® group.

Adverse Reactions: The safety population consisted of 363 dogs, with 182 receiving at least 1 dose of Vetmedin® and 181 dogs in the control group. Adverse events were seen in both treatment groups with many findings associated with the progression of MMVD and comorbidities consistent with the age of the enrolled dogs.

Cough was the most frequently reported adverse reaction in this study. This clinical finding is commonly reported in cases of MMVD, and the incidence was similar between treatment groups. Gastrointestinal upset (vomiting and diarrhea) was the most frequently reported non-cardiac adverse reaction associated with Vetmedin®.

Mortality rate, regardless of reason, prior to CHF was similar between the Vetmedin® and the control groups.

Table II.5. Cardiac Related Adverse Reactions[a]

Adverse Reaction	Vetmedin® Group (n=182)	Vehicle Control (n=181)
Cough	39 (21.4%)	42 (23.2%)
Lethargy	16 (8.8%)	13 (7.2%)
Inappetence	14 (7.7%)	13 (7.2%)
Tachypnea/panting	13 (7.1%)	12 (6.6%)
Arrhythmia	7 (3.9%)	3 (1.7%)
Collapse[b]	4 (2.2%)	2 (1.1%)
Dyspnea	4 (2.2%)	3 (1.7%)
Syncope[b]	0 (0.0%)	5 (2.8%)

Table II.6. Non-cardiac Adverse Reactions

Adverse Reaction	Vetmedin® Group (n=182)	Vehicle Control (n=181)
Musculoskeletal pain	24 (13.2%)	12 (6.6%)
Diarrhea	21 (11.5%)	16 (8.8%)
Vomiting	18 (9.9%)	24 (13.3%)
Seizure[b]	7 (3.8%)	2 (1.1%)
Pruritus	7 (3.9%)	3 (1.7%)
Lameness	7 (3.9%)	3 (1.7%)
Urinary tract infection	7 (3.9%)	2 (1.1%)
Restlessness	4 (2.2%)	0 (0%)

[a] These adverse reactions are commonly associated with cardiac disease, although some cases may have non-cardiac causes.

[b] Most cases of syncope and seizure were reported by the owner. These clinical signs can be difficult to differentiate.

Conclusions: This field study supports the effectiveness for Vetmedin® for the delay of onset of CHF in dogs with Stage B2 preclinical MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly. This study also supports the conclusion that Vetmedin® has an adequate safety profile in the target population.

2. US Field Study

Title: A Pivotal, Clinical Field Study Evaluating the Effectiveness of Pimobendan in Delaying the Onset of Congestive Heart Failure (CHF) in Dogs with ACVIM Stage B2 MMVD. (Study No. 2019035)

Study Dates: October 2020 to June 2025

Study Locations:

Leesburg, VA	Worthington, OH
Louisville, KY	Metairie, LA
Cockeysville, MD	Manchester, MO
Columbia, MD	Austin, TX
Annapolis, MD	Los Angeles, CA
Colorado Springs, CO	Rohnert Park, CA
Wheat Ridge, CO	Boulder, CO
Castle Rock, CO	

Study Design:

Objective: The study objective was to determine if chronic oral administration of pimobendan (Vetmedin® Chewable Tablets), in dogs with evidence of increased heart size secondary to Stage B2 preclinical MMVD, could delay the onset of CHF and cardiac death. This study was designed to support the results of the EPIC study (No. 2009045) described in Section II.B.1 above.

Study Animals: A total of 161 client-owned dogs were enrolled in the study and received treatment with Vetmedin®. Enrollment distribution included 43.5% females (intact and spayed) and 56.5% males (intact and neutered). The effectiveness population consisted of 125 dogs of various breeds. Mixed breeds were the most common breed, accounting for 52.8% of the effectiveness population, with 15.2% Cavalier King Charles Spaniels, 4.0% Havanese, 3.2% King Charles Spaniel, 3.2% Maltese, 2.4% Chihuahua, 2.4% Shetland Sheepdog, and 16.8% other breeds. Body weights ranged from 4.1 to 15.0 kg and age ranged from 6 to 16 years. All dogs were examined for evidence of Stage B2 preclinical MMVD (LA/Ao ratio ≥1.8) prior to enrollment.

Experimental Design: This study was a historically controlled, open-label, multi-center field study conducted in accordance with GCP guidelines. The historical control was derived from a subset of the control population enrolled in the EPIC study (No. 2009045; Section II.B.1) that met the enrollment criteria for this study. All enrolled client-owned dogs diagnosed with Stage B2 preclinical MMVD (LA/Ao ratio ≥1.8) received Vetmedin®.

Table II.7.Treatment Groups

Treatment Group	Dose	Safety Population	Effectiveness Population
Vetmedin® (pimobendan)	0.5 mg/kg/day	161	125

Drug Administration: Dogs were administered Vetmedin® 2.5 mg tablets at a target dose of 0.5 mg/kg per day for a maximum of 365 day ± 7 days. The calculated daily dose for each group was divided into two administrations,

adjusted to whole and half tablets, approximately 12 hours apart. The median dose administered was 0.48 mg/kg per day, with a range from 0.20 mg/kg to 0.62 mg/kg. Dogs were dosed according to Table II.8. The dose of study medication was not adjusted throughout the study.

Table II.8. Daily Dosing Chart (Vetmedin®)

Body Weight (kg)	First dose: Number of 2.5 mg tablets (morning)	Second dose: Number of 2.5 mg tablets (evening)
4.1-6.9	0.5	0.5
7.0-8.9	1	0.5
9.0-12.9	1	1
13.0-15.0	1.5	1.5

Measurements and Observations: Dogs were eligible for inclusion if the following Stage B2 preclinical MMVD criteria were met:

- Moderate to high intensity systolic heart murmur (grade ≥3/6)
- Echocardiographic evidence of MMVD defined as valvular lesions (leaflet thickening, valve prolapse, ruptured chordae tendineae)
- Presence of mitral regurgitation on Doppler echocardiogram
- Echocardiographic evidence of left atrial dilatation, measured by LA/Ao ratio (LA/Ao ratio ≥1.8)
- Radiographic evidence of cardiomegaly, measured by VHS (VHS >10.5)

Murmur grading, echocardiographic determination of LA/Ao ratio, and radiographic VHS measurements were conducted as described in the previous study (Section II.B.1 under Study Design, Measurements and Observations).

Dogs were excluded from the study if found to have: current or previous evidence of cardiogenic pulmonary edema, clinically significant tachyarrhythmias, current or previous evidence of clinically significant coughing, current or previous evidence of syncope, cardiac disease other than MMVD, known significant systemic or other organ related disease that would have limited the dog's life expectancy, evidence of pulmonary hypertension (right atrium to right ventricle (RA:RV) gradient >65 mmHg), or were pregnant or lactating female dogs. Dogs receiving treatment with a prohibited concomitant medication (Table II.3) were ineligible for screening unless one of the following criteria were met:

- Treatment was ≤14 days, and the dog had not received the medication within 30 days of Day 0.
- Treatment was >14 days, and the dog had not received the medication within ≥60 days of Day 0.

Before inclusion on Day 0, a case history was taken for each dog. A physical examination, hematology and blood chemistry evaluations, and other

examinations of cardiac function, including thoracic radiographs, echocardiography, and N-terminal pro-brain natriuretic peptide (NT-proBNP) evaluation, were performed. Dogs began study treatment on Day 0.

Physical examinations were conducted every 120 days following inclusion. Cardiac examinations were conducted at the end of study visit on Day 365 ± 7 or at the time of early termination from study.

The primary endpoint was individual treatment success or failure for each animal. A dog was considered a treatment success if it had no radiographic evidence of CHF at or before Day 365 AND did not develop malignant arrhythmias, syncope, significant coughing, and/or increased resting respiratory rate (RRR), requiring concomitant therapy at or before Day 365. A dog was considered a treatment failure if any of the following occurred at or before Day 365:

- It developed clinical signs of CHF with radiographic evidence documented and confirmed by an independent verification committee.
- It was euthanized or died in the absence of evidence of a non-cardiac cause of death.
- It developed malignant arrhythmias, syncope, significantly increased RRR and/or advanced coughing that required concomitant therapy in absence of radiographic CHF.

Five board-certified veterinary cardiologists served as the Independent Verification Committee (IVC) and reviewed inclusion and end of study criteria. The IVC were not associated with the study and were masked to treatment. Each case of CHF was verified by the IVC based on the radiographs alone. The endpoint confirmation was evaluated by three IVC members with final results dependent on a minimum of 2/3 majority decision. Only if the IVC verified CHF was the dog considered to have reached the primary endpoint.

Study Duration: The total study duration was 2 years and 9 months. The recruitment phase took approximately 1 year and 9 months, and each dog was treated for up to 1 year. The last patient completed its end of study visit in August 2024.

Statistical Methods:

Analysis Populations: Sample size was calculated based on the primary parameter and the need for the lower 95% confidence interval to have been at least 54%. In the study used for historical control (EPIC study (No. 2009045; Section II.B.1)), the treatment success/failure criteria at 365 days from cases enrolled at US sites were applied and resulted in a success rate of 80% with a lower 80% confidence interval of 72%. Assuming a true success rate of at least 72%, simulations indicated that 98 evaluable dogs would provide at least 90% power to achieve the lower 95% confidence of 54%. In the current study, the safety population consisted of 161 dogs that received at least 1 dose of Vetmedin®. The effectiveness population

consisted of 125 from the safety population which did not have major violations to the inclusion and exclusion criteria.

The experimental unit was the individual animal. The individual treatment success/failure data were analyzed using the GLIMMIX procedure of SAS Version 9.4 with a binomial distribution and logit link. The model was an intercept model with site as a random effect. The percent of treatment successes and the lower 95% confidence limit was calculated by back transforming the logit estimates of the intercept and its lower 95% confidence limit based on the two-sided test at alpha=0.05. The treatment was considered effective if the lower bound of the 95% confidence interval was greater than or equal to 54% and the estimated success rate for pimobendan was greater than or equal to 65%.

Results: Of the 125 dogs included in the effectiveness population:

- 99 dogs successfully reached their Day 365 visit with no evidence of disease progression, while
- 26 dogs met failure criteria on or prior to their Day 365 visit. Of the 26 failures:
    - 13 dogs developed clinical signs of CHF with radiographic evidence,
    - 3 dogs died without evidence of death due to a non-cardiac cause, and
    - 10 dogs developed syncope, and/or increased RRR, or advanced coughing requiring concomitant therapy without radiographic evidence of CHF.

For the primary endpoint, the estimated treatment success rate was 79.2% (95% confidence interval 70.3 to 85.9%). The study's success criteria were met, as the lower bound of the 95% confidence interval for the success rate (70.3%) was well above the pre-specified threshold of 54%.

Adverse Reactions: The safety population consisted of 161 dogs receiving at least 1 dose of Vetmedin®. Adverse reactions were reported in 138 dogs (85.7%) with many findings associated with the progression of MMVD and comorbidities consistent with the age of the enrolled dogs.

Adverse reactions identified in this study were similar to the first study with many findings associated with MMVD and age-related comorbidities. Cough was the most frequently reported cardiac related adverse reaction and gastrointestinal upset (vomiting and diarrhea) was the most frequently reported non-cardiac adverse reaction associated with Vetmedin®.

One dog was removed from the study because of drug intolerance associated with gastrointestinal signs (lethargy, vomiting, diarrhea).

Chordae tendineae rupture occurred in three dogs receiving Vetmedin® in this study, resulting in the euthanasia of one dog. In the EPIC study (No. 2009045; Section II.B.1), chordae tendinea rupture was observed in three control dogs and in zero Vetmedin®-treated dogs.

In this study, 14 Vetmedin®-treated dogs died or were euthanized by Day 365; 9 for cardiac related reasons and 6 for reasons unrelated to MMVD or treatment with Vetmedin®.

Table II.9. Cardiac Related Adverse Reactions[a]

Adverse Reaction	Vetmedin® (n=161)
Cough	48 (29.8%)
Inappetence	30 (18.6%)
Lethargy	25 (15.5%)
Tachypnea/panting	17 (10.6%)
Arrhythmia	13 (8.1%)
Dyspnea	6 (3.7%)
Syncope[b]	5 (3.1%)
Collapse[b]	2 (1.2%)

Table II.10. Non-cardiac Adverse Reactions

Adverse Reaction	Vetmedin® (n=161)
Vomiting	59 (36.6%)
Diarrhea	53 (32.9%)
Musculoskeletal pain	12 (7.5%)
Lameness	10 (6.2%)
Dermal mass	9 (5.6%)
Polydipsia	9 (5.6%)
Pruritus	7 (4.3%)
Polyuria	6 (3.7%)
Urinary tract infection	6 (3.7%)
Restlessness	4 (2.5%)
Seizure[b]	3 (1.9%)

[a] These adverse reactions are commonly associated with cardiac disease, although some cases may have non-cardiac causes.

[b] Most cases of collapse, syncope, and seizure were reported by the owner. These clinical signs can be difficult to differentiate.

Conclusions: This study demonstrates the effectiveness of Vetmedin® for the delay of onset of CHF in a subset of dogs with Stage B2 preclinical MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly (LA/Ao ≥1.8). This study also supports the conclusion that Vetmedin® has an adequate safety profile in the target population.

III. TARGET ANIMAL SAFETY

The FDA did not require target animal safety studies for this supplemental approval. The FOI Summary for the original NADA 141-273 dated April 30, 2007, contains a summary of the target animal safety study for dogs.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Vetmedin®:

Not for use in humans.
Keep this and all medications out of reach of children.
Consult a physician in case of accidental ingestion by humans.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the FD&C Act and 21 CFR part 514. The data demonstrate that Vetmedin®, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to diagnose Stage B2 preclinical MMVD and to monitor for and respond to adverse reactions.

B. Exclusivity

This supplemental approval for Vetmedin® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indication for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical MMVD. Stage B2 preclinical MMVD refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval required a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.