

Date of Approval: June 16, 2022

# FREEDOM OF INFORMATION SUMMARY

## APPLICATION FOR CONDITIONAL APPROVAL

Application Number 141-556

Vetmedin<sup>®</sup>-CA1

(pimobendan)

Chewable Tablets

Dogs

Vetmedin<sup>®</sup>-CA1 is indicated for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease (2019 ACVIM Consensus Statement<sup>1</sup>).

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.

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<sup>1</sup> 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.

## Executive Summary

Vetmedin<sup>®</sup>-CA1 (pimobendan) is conditionally approved for the delay of onset of congestive heart failure 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 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.

FDA determined that Vetmedin<sup>®</sup>-CA1 is eligible for conditional approval for the labeled use under section 571(a)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because the drug controls a serious or life-threatening disease in dogs, addresses an unmet animal health need, and demonstrating effectiveness would require complex or particularly difficult studies. An animal drug that meets these criteria is eligible for conditional approval.

A conditionally approved animal drug has been shown to be safe and have a reasonable expectation of effectiveness. During the conditional approval period, the sponsor can legally market the drug for the labeled use while collecting the remaining effectiveness data. The conditional approval is valid for one year. The sponsor can ask FDA to renew the conditional approval annually for up to four more years, for a total of five years of conditional approval. To receive a renewal from FDA, the sponsor must show active progress toward proving substantial evidence of effectiveness for full approval.

Vetmedin<sup>®</sup> is already fully approved under New Animal Drug Application (NADA) 141-273 for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to clinical MMVD or dilated cardiomyopathy (DCM). The drug is for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

Vetmedin<sup>®</sup> and Vetmedin<sup>®</sup>-CA1 contain the same active ingredient, pimobendan, at the same dose, but will be marketed separately with two separate labels, and each drug has a unique application number.

| <b>Proprietary Name</b>    | <b>Established Name</b> | <b>Application Type and Number</b>              | <b>Sponsor</b>                               |
|----------------------------|-------------------------|---|--|
| Vetmedin <sup>®</sup> -CA1 | pimobendan              | Conditional Approval Application Number 141-556 | Boehringer Ingelheim Animal Health USA, Inc. |

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 Reasonable Expectation of Effectiveness**

The sponsor conducted a long-term, multi-center field study in client-owned dogs that had cardiomegaly secondary to Stage B2 preclinical MMVD. Enrolled dogs weighed 15 kgs (33 lbs) or less, were of both sexes, and were between 6 and 17 years of age. Dogs were eligible for inclusion if the following Stage B2 preclinical MMVD criteria were met: moderate to high intensity systolic heart murmur (grade  $\geq$  3/6); echocardiographic evidence of MMVD, mitral regurgitation, and left atrial dilatation; increased left ventricular internal-diastolic diameter; and radiographic evidence of cardiomegaly. Various breeds were represented in the study, with Cavalier King Charles Spaniels being the most common breed. The study lasted over 4 years.

Enrolled dogs had physical and cardiac examinations on Day 0 and at several other timepoints throughout the study. On Day 0, enrolled dogs were started on either Vetmedin<sup>®</sup>-CA1 or a control chewable tablet with no active ingredient (vehicle). The primary endpoint was when a dog developed left-sided congestive heart failure, was euthanized due to cardiac disease, or died due to cardiac disease. Reasonable expectation of effectiveness was determined based on the length of time from first treatment to when the dog reached the primary endpoint. The median time to the primary endpoint was 1,228 days in the Vetmedin<sup>®</sup>-CA1 group compared to 761 days in the control group, a difference of 467 days (15.6 months).

In addition, when all causes of mortality were analyzed (which included dogs with and without congestive heart failure), dogs in the Vetmedin<sup>®</sup>-CA1 group had a prolonged survival time compared to the control group (1,059 days and 889 days, respectively). Baseline heart size was also compared to the heart size 5 to 6 weeks after the study started. Dogs treated with Vetmedin<sup>®</sup>-CA1 had a decreased heart size, as measured by left ventricular enlargement, 5 to 6 weeks after starting the drug.

Adverse reactions were seen in dogs in both the Vetmedin<sup>®</sup>-CA1 and control groups. Many of these reactions are associated with the natural progression of MMVD and with comorbidities consistent with the age of enrolled dogs. The median time to the primary endpoint was 38% longer in the Vetmedin<sup>®</sup>-CA1 group, but despite this longer duration on study, the incidence of reported adverse reactions was similar between both groups.

Cough was the most frequently reported adverse reaction. This clinical finding is commonly reported in dogs with MMVD and the incidence was similar between the Vetmedin<sup>®</sup>-CA1 and control groups. Lethargy, inappetence, tachypnea, collapse, arrhythmia, and syncope were reported in dogs treated with Vetmedin<sup>®</sup>-CA1 and may also be associated with the progression of MMVD. Adverse reactions unrelated to the progression of MMVD in dogs treated with Vetmedin<sup>®</sup>-CA1 included diarrhea, vomiting, pain, lameness, arthritis, urinary tract infection, and seizure.

The results of the field study demonstrate that there is a reasonable expectation of effectiveness for Vetmedin<sup>®</sup>-CA1 to delay the onset of congestive heart failure in dogs with Stage B2 preclinical MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly. Although this study generated robust data, it did not have all the characteristics of an adequate and well-controlled study to support substantial evidence of effectiveness. This study is acceptable to support reasonable expectation of effectiveness for conditional approval.

FDA did not require new safety studies in dogs for this conditional approval. The dose of pimobendan in Vetmedin<sup>®</sup>-CA1 is identical to the dose in Vetmedin<sup>®</sup> (which is fully approved under NADA 141-273); therefore, the safety of the drug in dogs is supported by the target animal safety studies conducted for the approval of NADA 141-273. Also, the field study conducted for this conditional approval showed that Vetmedin<sup>®</sup>-CA1 has an adequate safety profile in dogs with Stage B2 preclinical MMVD.

**Other Safety Information**

Vetmedin<sup>®</sup>-CA1 should not be administered to dogs with hypertrophic cardiomyopathy, aortic stenosis, or any other clinical condition where increased cardiac output is inappropriate due to functional or anatomical reasons. Vetmedin<sup>®</sup>-CA1 should also not be administered to dogs before they develop cardiomegaly, as this causes an increased risk of cardiac pathology associated with exaggerated hemodynamic responses.

**Conclusions**

Based on the data submitted by the sponsor for the conditional approval of Vetmedin<sup>®</sup>-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the labeling.

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**I. GENERAL INFORMATION**

**A. File Number**

Application Number 141-556

**B. Sponsor**

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

Drug Labeler Code: 000010

**C. Proprietary Name**

Vetmedin®-CA1

**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 mg, 2.5 mg, 5 mg, and 10 mg

**H. How Supplied**

50 tablets per bottle

**I. Dispensing Status**

Prescription (Rx)

**J. Dosage Regimen**

Vetmedin®-CA1 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/Class**

Dogs

## **M. Indication**

Vetmedin<sup>®</sup>-CA1 (pimobendan) is indicated for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical myxomatous mitral valve disease (2019 ACVIM Consensus Statement<sup>1</sup>).

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**

**Conditional Dose:** The conditional dose for the indication “for the delay of onset of congestive heart failure in dogs with preclinical MMVD (2019 ACVIM Consensus Statement<sup>1</sup>)” is a total daily dose of 0.23 mg/lb (0.5 mg/kg) divided into 2 portions, administered orally, approximately 12 hours apart. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional dose.

### **A. Dosage Characterization**

The conditionally approved dose is the same as that of Vetmedin<sup>®</sup> (pimobendan), previously approved under NADA 141-273, for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to clinical MMVD or DCM. Vetmedin<sup>®</sup> is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

The Freedom of Information (FOI) Summary for the original approval of NADA 141-273, dated April 30, 2007, contains dosage characterization information for dogs.

### **B. Reasonable Expectation of Effectiveness**

Reasonable expectation of effectiveness for Vetmedin<sup>®</sup>-CA1 (pimobendan) for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical MMVD (2019 ACVIM Consensus Statement<sup>1</sup>) is based on the results of the field study entitled: Evaluation of pimobendan in dogs with cardiomegaly caused by preclinical mitral valve disease – EPIC (Study No. 2009045).

Stage B2 preclinical MMVD refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.

Current definitions use the term MMVD when describing mitral valve specific canine acquired heart disease.<sup>2,3</sup> The historical term of atrioventricular valvular insufficiency (AVVI) is considered synonymous with MMVD.

**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

Columbus, OH  
Blacksburg, VA  
Overland Park, KS  
Gilbert, AZ  
Los Angeles, CA (2 sites)  
New York, NY  
College Station, TX  
Raleigh, NC  
Ithaca, NY  
Englewood, CO  
Chicago, IL  
Rohnert Park, CA  
Gainesville, FL  
Philadelphia, PA  
Towson, MD  
North Grafton, MA  
Tampa, FL  
Madison, WI

International

Moorabbin, Australia  
Guelph, Ontario, Canada  
Meaux, France  
Villars Les Dombes, France  
Munich, Germany  
Duisburg, Germany  
Wiesloch, Germany  
Samarate, Italy  
Danderyd, Sweden  
Kanagawa, Japan (2 sites)  
Utrecht, Netherlands  
Murcia, Spain  
Uppsala, Sweden  
Hatfield, Herts, United Kingdom  
Gloucestershire, United Kingdom  
Etwall, Derby, United Kingdom

**Study Design:**

**Objective:** The study objective was to determine whether chronic oral administration of pimobendan (Vetmedin<sup>®</sup>-CA1), in dogs with evidence of increased heart size secondary to Stage B2 preclinical MMVD, could delay the onset of signs of congestive heart failure.

**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

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<sup>2</sup> 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.

<sup>3</sup> Atkins, C., et al. (2009) Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. *J Vet Intern Med.* 23(6):1142-1150.



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 Practices guidelines. Client-owned dogs diagnosed with MMVD were enrolled and randomized in a 1:1 ratio to receive either Vetmedin®-CA1 or a vehicle control chewable tablet.

**Table II.1: Treatment Groups**

| <b>Treatment Group</b>     | <b>Dose</b>   | <b>Safety Population</b> | <b>Effectiveness Population</b> |
|----------------------------|---------------|--------------------------|---------------------------------|
| Vetmedin®-CA1 (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®-CA1 2.5 mg tablets at a target dose of 0.5 mg/kg per day. The median dose of Vetmedin®-CA1 administered to dogs in the Vetmedin®-CA1 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®-CA1 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®-CA1 or Control)**

| <b>Body Weight (kg)</b> | <b>First dose: Number of 2.5 mg tablets (morning)</b> | <b>Second dose: Number of 2.5 mg tablets (evening)</b> |
|-------------------------|---|--|
| 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  $\geq$  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 left atrial-to-aortic root diameter ratio (LA/Ao ratio  $\geq$  1.6)
- Increased left ventricular internal-diastolic diameter, normalized for body weight (LVIDDN  $\geq$  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 1-6:

- 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:

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

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.3) 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.3: Prohibited Concomitant Medications**

| <b>Prohibited Concomitant Medications</b>  |
|--|
| 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 congestive heart failure, or euthanasia for a cardiac disease related reason, or death presumed to be cardiac in origin. A dog was considered to have left-sided congestive heart failure when there was radiographic evidence of cardiogenic pulmonary edema as indicated by an interstitial or alveolar pattern in conjunction with left sided cardiomegaly. 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 congestive heart failure 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 congestive heart failure was the dog considered to have reached the primary endpoint.

Secondary variables included overall survival time (all-cause mortality) and the effect of pimobendan on the heart size on Day 35  $\pm$  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 and 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 (pimobendan n = 182; control n = 181) that were randomized and received at least one dose of study medication. The effectiveness population consisted of 353 dogs (pimobendan n = 178; control n = 175) from the safety population which did not have major violations to the inclusion and exclusion criteria.

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 compare the survival curves between 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 (2-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 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 - 0.9051) estimated from the Cox model in favor of the pimobendan group. The p-value for treatment comparison was less than the nominal alpha level of 0.0244 per O'Brien-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 353 dogs included in the effectiveness population in the final analysis, 74 of 178 dogs in the pimobendan group and 88 of 175 dogs in the control group reached the primary endpoint. There were 59 cases with verified congestive heart failure and 15 cases of death or euthanasia for cardiac disease related reason in the pimobendan group, and 76 cases with verified congestive heart failure and 12 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 survival curves between the two treatment groups had a p-value of 0.0028. The median (95% confidence interval) time to the primary endpoint was 1228 (856, high end not estimable) days in the pimobendan group, and 761 (637 – 875) days in the control group. This translates to a difference of 467 days (15.6 months) in the median time to the primary endpoint in favor of the pimobendan group. The hazard ratio (95% confidence interval) from the Cox Proportional hazard model was 0.6259 (0.4589 - 0.8537). 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 pimobendan 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<sup>®</sup>-CA1 group. The median survival time was 1059 days in the Vetmedin<sup>®</sup>-CA1 group compared to 889 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<sup>®</sup>-CA1 group.

**Adverse Reactions:** 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.

The median time to the primary endpoint (development of left-sided congestive heart failure or cardiac death/euthanasia) was 38% longer in the Vetmedin<sup>®</sup>-CA1 group. Despite the longer duration on study, the incidence of reported adverse reactions was similar between treatment groups.

Cough was the most frequently reported adverse reaction. This clinical finding is commonly reported in cases of MMVD and the incidence was similar between treatment groups. Lethargy, inappetence, tachypnea, collapse, arrhythmia, and syncope may also be associated with the progression of MMVD and were reported in dogs receiving Vetmedin<sup>®</sup>-CA1.

Adverse reactions not related to disease progression in dogs receiving Vetmedin<sup>®</sup>-CA1 included diarrhea, vomiting, pain, lameness, arthritis, urinary tract infection, and seizure.

Mortality rate, regardless of reason, prior to congestive heart failure was similar between the Vetmedin<sup>®</sup>-CA1 and the control groups.

**Conclusions:** The results of this study demonstrate reasonable expectation of effectiveness for Vetmedin<sup>®</sup>-CA1, administered at the label dose of 0.23 mg/lb (0.5 mg/kg) body weight per day, for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly (2019 ACVIM Consensus Statement<sup>1</sup>). This study also supports the conclusion that Vetmedin<sup>®</sup>-CA1 has an adequate safety profile in the target population.

### **III. TARGET ANIMAL SAFETY**

As the dosage of pimobendan in Vetmedin<sup>®</sup>-CA1 is identical to that of Vetmedin<sup>®</sup> (pimobendan) for dogs, approved under NADA 141-273, the target animal safety for Vetmedin<sup>®</sup>-CA1 is supported by the target animal safety studies conducted for the approval of Vetmedin<sup>®</sup>. Refer to the FOI summary for Vetmedin<sup>®</sup> (NADA 141-273) for detailed information on these studies.

### **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, CVM 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<sup>®</sup>-CA1:

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 application satisfy the requirements of section 571(b) of the FD&C Act. The data demonstrate that Vetmedin<sup>®</sup>-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the delay of onset of congestive heart failure in dogs with Stage B2 preclinical MMVD (2019 ACVIM Consensus Statement<sup>1</sup>). Stage B2 preclinical MMVD refers to dogs with asymptomatic MMVD that have a moderate or loud mitral murmur due to mitral regurgitation and cardiomegaly.

#### **A. Conditional Approval Eligibility**

In 2018, the legislation reauthorizing FDA's animal drug user fee program (Animal Drug User Fee Program, or ADUFA, IV) expanded the conditional approval pathway to allow certain additional new animal drugs that are not Minor Use/Minor Species (MUMS) drugs to be eligible for conditional approval. As provided in section 571(a)(1)(A)(ii) of the FD&C Act, as amended by ADUFA IV, to qualify for conditional approval, the non-MUMS new animal drug must meet the following two criteria:

1. The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND
2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

Vetmedin<sup>®</sup>-CA1 was determined to be eligible for conditional approval under these provisions because it controls a serious or life-threatening disease or condition, addresses an unmet animal health need, and the demonstration of effectiveness requires a complex or particularly difficult study or studies. Congestive heart failure is a disease or condition associated with morbidity that has substantial impact on day-to-day functioning in the target animal. Therefore, the conditionally approved use to delay the onset of congestive heart failure in dogs with Stage B2 preclinical MMVD addresses a serious or life-threatening disease or condition. The delay in onset of congestive heart failure in dogs with Stage B2 preclinical MMVD in dogs was also determined to be an unmet animal health need because there is no approved animal drug currently being marketed in the United States for this use in dogs. Finally, based on the need for a long study duration to establish effectiveness, it was determined that the demonstration of effectiveness requires a complex or particularly difficult study or studies.

#### **B. Marketing Status**

Vetmedin<sup>®</sup>-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose and stage MMVD.

#### **C. Exclusive Marketing Rights**

Vetmedin<sup>®</sup>-CA1 as approved in our approval letter, does not qualify for exclusive marketing rights under section 573(c) of the FD&C Act because it is not a designated new animal drug under section 573(a) of the FD&C Act.

#### **D. Patent Information**

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