Date of Approval: April 30, 2007

FREEDOM OF INFORMATION SUMMARY

CORRECTED ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-273

VETMEDIN

Pimobendan
Chewable Tablets

Dogs

VETMEDIN (pimobendan) is indicated for the management of the signs of mild, moderate, or severe (modified New York Heart Association (NYHA) Class II, III, or IV) congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI) 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.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-273
B. Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, MO 64506-2002 Drug Labeler Code: 000010
C. Proprietary Name(s):	VETMEDIN
D. Established Name(s):	Pimobendan
E. Pharmacological Category:	Inodilator (calcium sensitizer and phosphodiesterase III inhibitor)
F. Dosage Form(s):	Chewable tablet
G. Amount of Active Ingredient(s):	1.25, 2.5, and 5 mg pimobendan per tablet
H. How Supplied:	50 tablets per bottle
I. How Dispensed:	Rx
J. Dosage(s):	VETMEDIN 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(s) of Administration:	Oral
L. Species/Class(es):	Dogs

M. Indication(s):

VETMEDIN (pimobendan) is indicated for the management of the signs of mild, moderate, or severe (modified NYHA Class II[a], III[b], or IV[c]) congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI) 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.

[a] A dog with modified New York Heart Association (NYHA) Class II heart failure has fatigue, shortness of breath, coughing, etc. apparent when ordinary exercise is exceeded.

[b] A dog with modified NYHA Class III heart failure is comfortable at rest, but exercise capacity is minimal.

[c] A dog with modified NYHA Class IV heart failure has no capacity for exercise and disabling clinical signs are present even at rest.

II. EFFECTIVENESS:

A. Dosage Characterization:

Pimobendan's effect on cardiac contractility was tested at several single oral doses (0.1, 0.25, 0.5 and 1.0 mg/kg). Normal dogs were instrumented with left ventricular (LV) pressure transducers. The maximum rate of rise of the LV pressure (LV dP/dtmax) was calculated. This ratio is a measure of contractility of the heart. Pimobendan increased LV dP/dtmax at all doses tested in a dose dependent manner up to a dose of 0.5 mg/kg. No further increase was seen at 1.0 mg/kg compared to 0.5 mg/kg. The effect was still present eight hours after dosing. The time to maximum increase was shorter with the higher doses.

An effective dose of pimobendan was determined in a European field study of dogs with naturally occurring heart failure. In this study, a liquid formulation of pimobendan was administered at a total daily dose of 0.2 to 0.6 mg/kg per day (0.1 to 0.3 mg/kg administered twice daily). A total of 45 dogs were evaluated: 24 with dilated cardiomyopathy (DCM), 18 with atrioventricular valvular insufficiency (AVVI), and 3 with unspecified etiology. An optimal dose was determined by looking at the percentage of dogs at each dose that improved or needed to move on to a higher dose. Initially, dogs received a dose of 0.2 mg/kg per day, in two divided doses. The dogs were examined every 7 to 10 days of treatment and thereafter at the same interval if the dose was to be increased. Once the evaluation was considered to be "good," the dog would stay at that dose. The final evaluation was done after the dog had been on the optimal dose for two weeks. Improvement was based on general clinical impression. The lowest dosage (0.2 mg/kg/day) was sufficient in only 13.3% of the cases (6 dogs), whereas in 28.9% of the cases (13 dogs) the highest dose (0.6 mg/kg/day) was necessary. For 57.8% of the cases (26 dogs), the middle dose (0.4 mg/kg/day) was sufficient for improvement. This study supported a pimobendan total daily dose range of 0.4 mg/kg to 0.6 mg/kg administered at 0.2 to 0.3 mg/kg twice daily.

Two additional European field studies in dogs with naturally occurring heart failure were conducted. Both studies compared the effectiveness of 0.4 to 0.6 mg/kg/day of pimobendan capsules (administered at 0.2 to 0.3 mg/kg twice daily) with that of an angiotensin converting enzyme (ACE) inhibitor approved for veterinary use in Europe. In the first of these two field studies, a total of 105 dogs (81 with DCM and 24 with AVVI) were evaluated for a 4-week treatment period. In the second of these two field studies, a total of 76 dogs with AVVI were evaluated for an 8-week treatment period. In each of these two studies, the pimobendan treatment group had greater improvement in heart failure classification and overall effectiveness than the ACE inhibitor treatment group. In optional follow-up studies with fewer restrictions on concurrent medication, median survival time was longer for dogs that received pimobendan compared to dogs that did not receive pimobendan.

Based on these studies, 0.5 mg/kg/day was selected as the appropriate dosage for VETMEDIN chewable tablets.

B. Substantial Evidence:

1. Pivotal Field Study

a. Title: The Clinical Efficacy of VETMEDIN (pimobendan) in Dogs Suffering from Congestive Heart Failure, Study Number: 6150-0990-00C-087

b. Investigators: See Table 1.

Table 1: Investigators and Enrolling Field Study Sites

Site[a]	Investigator	Clinic
74	Dr. Audrey Cook	Veterinary Internal Medicine, Newport News, VA
75	Dr. Kyle Brayley	Veterinary Medical Specialists of Houston, Houston, TX
76	Dr. Judith Parker	Pima Pet Clinic, Tucson, AZ
77	Dr. Justin Straus	Animal Emergency & Referral Center, West Caldwell, NJ
78	Dr. Richard Kienle	Bay Area Veterinary Specialists, San Leandro, CA
79	Dr. Mitch Crystal	North Florida Veterinary Specialists, Jacksonville, FL
81	Dr. Nancy Morris	Mass Veterinary Cardiology Services, Pembroke, MA
82	Dr. Craig Maretzki	San Francisco Veterinary Specialists, San Francisco, CA
83	Dr. Aaron Wey	VCA Emergency Animal Hospital, San Diego, CA
84	Dr. Gary Wood	Cardiology Northwest, Portland, OR
85	Dr. Steven Ettinger	California Animal Hospital, Los Angeles, CA
86	Dr. Linda Lehmkuhl	MedVet, Worthington, OH
87	Dr. Carroll Loyer	Veterinary Referral Center of Colorado, Englewood, CO
88	Dr. Tacy Rupp	Veterinary Specialists of South Florida, Cooper City, FL
89	Dr. Don Schrope	Oradell Animal Hospital, Paramus, NJ

Site[a]	Investigator	Clinic
90	Dr. Doug Santen	Alameda East Veterinary Hospital, Denver, CO
91	Dr. Edward Fallin	Veterinary Referral and Critical Care, Manakin-Sabot, VA
92	Dr. Kathy Huff	The CARE Center, Blue Ash, OH
93	Dr. Jeff Dennis	Veterinary Specialty & Emergency Center of KC, Overland Park, KS
94	Dr. Darlene Blischok	Georgia Veterinary Specialists, Atlanta, GA
95	Dr. Steve Rosenthal	Chesapeake Veterinary Cardiology Associates, Towson, MD
96	Dr. William Tyrrell	Chesapeake Veterinary Cardiology Associates, Leesburg, VA

[a] Site 80 did not enroll any dogs in the study.

The veterinary radiologist Dr. Loren Shaiken, Fairway, KS, evaluated thoracic radiographs for pulmonary edema, pleural effusion, and vertebral heart size. The veterinary pathologist Dr. Sanford Bishop, Glenville, NC, provided cardiac histopathology.

c. Study Design: Multi-site, double-masked, randomized, non-inferiority comparison field study

1) Objective: The study was designed to evaluate the safety and effectiveness of VETMEDIN (pimobendan) compared to the active control enalapril maleate in the management of congestive heart failure (CHF) associated with atrioventricular valvular insufficiency (AVVI) or dilated cardiomyopathy (DCM) in dogs under clinical conditions.

2) Study Animals: The study enrolled 355 client-owned dogs of various breeds, ranging in weight from 3.3 to 191 pounds, ranging in age from 1 to 17 years, 52% male and 48% female, and diagnosed with CHF attributable to AVVI (256 dogs, 72%) or DCM (99 dogs, 28%). To be eligible, dogs had to have a modified New York Heart Association (NYHA) heart failure (HF) Classification of II, III, or IV, defined as follows:

Class I: Exercise capacity limited only during strenuous, athletic activity;
Class II: Fatigue, shortness of breath, coughing, etc. apparent when ordinary exercise is exceeded;
Class III: Comfortable at rest, but exercise capacity is minimal;
Class IV: No capacity for exercise. Disabling clinical signs are present even at rest.

Additional eligibility criteria included: radiographic evidence of congestive heart failure (pulmonary edema and cardiomegaly) in dogs with Class III or IV HF, and echocardiographic confirmation of the diagnoses of AVVI and DCM. AVVI dogs had to have 2-D or M-mode evidence of thickened valve leaflets, presence of moderate to severe atrioventricular (AV) valvular regurgitation, moderate to severe left atrial enlargement, and lack of severe left ventricular dilation. DCM dogs were to have a shortening fraction of < 25%. Dogs were excluded from entering the study if they were younger than 6 months of age; lactating or pregnant; had congenital heart disease, asymptomatic heart disease (modified NYHA HF Class I), hypertrophic cardiomyopathy; chronic, moderate-to-severe pulmonary, bronchial, or tracheal disease; severe endocrine or metabolic disease (except hypothyroidism if on a stable dose of levothyroxine for more than 2 weeks); a positive heartworm antigen test, a serum creatinine > 2.5 mg/dL; if they had received digitalis glycosides or other positive inotropic drugs within seven days prior to enrollment; or if they received any treatment for CHF, other than furosemide, for more than 3 days prior to enrollment.

3) Treatment Groups: Table 2 provides the baseline characteristics for the two treatment groups.

Table 2: Demographics of Dogs Enrolled in the Pivotal Field Study

Demographics in the VETMEDIN Group	**Demographics in the Active Control Group**
175 dogs that received at least one dose of pimobendan 49% male, 51% female 72% had AVVI, 28% had DCM Age: 1-16 years, mean 10.2 years Wt: 4.5-191 lbs, mean 38.4 lbs	180 dogs that received at least one dose of enalapril maleate 55% male, 45% female 72% had AVVI, 28% had DCM Age: 4-17 years, mean 10.5 years Wt: 3.3-161 lbs, mean 40.1 lbs
36.6% Class II HF 45.7% Class III HF 17.7% Class IV HF	30.6% Class II HF 48.3% Class III HF 21.1% Class IV HF
The most common breeds: Mixed breed (30 dogs) Doberman Pinscher (24) Cocker Spaniel (14) Miniature/Toy Poodle (11) Maltese (11) Cavalier King Charles Spaniel (8) Miniature Schnauzer (7)	The most common breeds: Mixed breed (38 dogs) Doberman Pinscher (21) Miniature/Toy Poodle (10) Chihuahua (9) Cocker Spaniel (8) Maltese (8) Dachshund (6)
Of the 49 dogs with DCM: 14 had atrial fibrillation 23 were Doberman Pinschers	Of the 50 dogs with DCM: 10 had atrial fibrillation 20 were Doberman Pinschers

4) Drug Administration:
In the VETMEDIN group, pimobendan was administered at 0.5 mg/kg per day, given in divided doses that were not necessarily equal, approximately 12 hours apart (morning and evening), using a suitable combination of 1.25, 2.5, and/or 5 mg chewable tablets to achieve the 0.5 mg/kg daily dose.

In the active control group, enalapril maleate (ENACARD) was administered at 0.5 mg/kg once daily. Investigators optionally increased the dose to 0.5 mg/kg twice daily based on response during the first two weeks of treatment while at 0.5 mg/kg once daily.

In both treatment groups, furosemide was administered to dogs as needed to manage congestion. There were no restrictions on the dose of furosemide. Investigators were encouraged to titrate furosemide to the lowest effective dose needed to control signs of congestion.

The protocol for digoxin administration was different between treatment groups for dogs with DCM. See Table 3.

Table 3: Digoxin Administration

Treatment Group	**Digoxin use in Dogs with AVVI**	**Digoxin use in Dogs with DCM**
VETMEDIN	optional [a]	optional [a]
Active Control	optional [a]	required

[a] Digoxin was allowed for the treatment of supraventricular arrhythmias.

Atenolol or propranolol was permitted as add-on therapy when digoxin was ineffective in the control of supraventricular tachyarrhythmias.

5) Measurements and Observations:
Pretreatment procedures, to assess eligibility and provide baseline data, included: physical examination, heart murmur grade, and body weight; modified NYHA HF Class (Heart Insufficiency Score); ratings for cough, respiratory effort, nocturnal dyspnea, appetite, water consumption, attitude, vomiting, diarrhea, and activity level; clinical pathology (hematology, clinical chemistry, and heartworm test); electrocardiogram (ECG, for the presence and type of arrhythmias); echocardiogram; and thoracic radiographs (for assessment of pulmonary edema (Pulmonary Edema Score), pleural effusion, and vertebral heart size (VHS) by the masked veterinary radiologist).

Heart Insufficiency was scored as follows:

1 = modified NYHA Class I HF
2 = modified NYHA Class II HF
3 = modified NYHA Class III HF
4 = modified NYHA Class IV HF

Pulmonary Edema was scored as follows:

1 = No pulmonary edema
2 = Mild interstitial density
3 = Moderate interstitial density
4 = Interstitial and alveolar pattern
5 = Severe, diffuse alveolar pattern

The vertebral heart size (VHS) is a measurement of heart size proportionate to the size of the dog. VHS is determined from a lateral radiographic view of the chest, and is a sum of the long and short axes of the heart, represented by lengths of thoracic vertebrae. The normal range of VHS is 8.5 to 10.5 vertebrae.

Dogs began treatment on Day 1 of the study. Dogs were scheduled to be rechecked at Day 8±3, Day 29±3, and Day 56±4, for repeat physical examinations, heart murmur grade, weight, Heart Insufficiency Score, ratings for attitude, cough, activity, and water consumption, reporting of side effects, clinical pathology (hematology, clinical chemistry, and digoxin level if applicable), ECGs, and dose adjustments in furosemide (if applicable). Owners recorded observations on a daily treatment record. Dogs were seen at additional visits as needed for veterinary care. At the Day 29 and 56 visits, thoracic radiographs (with evaluations for Pulmonary Edema Score, pleural effusion, and VHS) were repeated, and Overall Clinical Effectiveness (OCE) was scored by the investigator based on physical examination, radiography, ECG, and clinical pathology.

Overall Clinical Effectiveness (OCE) was scored as follows:

1 = Clinical condition greatly improved with treatment
2 = Clinical condition moderately improved with treatment
3 = Clinical condition slightly improved with treatment
4 = Clinical condition not improved or worsened with treatment

The pivotal measure of effectiveness in each treatment group was the percent of dogs that achieved Treatment Success at Day 29 (Success Rate). A dog was considered to be a Treatment Success if it met two of the three following criteria:

The Heart Insufficiency Score decreased between Day 1 and Day 29
The Pulmonary Edema Score decreased between Day 1 and Day 29
The Day 29 Overall Clinical Effectiveness Score was 1, 2, or 3

6) Statistical Methods: Treatment Success was analyzed using a generalized linear mixed model. A 95% one-sided confidence limit for the difference in success rates for the two treatment groups was calculated from the model based estimates of the success rates and the standard error of the difference in success rates. The hypothesis of non-inferiority of VETMEDIN compared to active control was to be accepted if the lower 95% confidence limit for the difference in percents of treatment success, percent success in the VETMEDIN group minus percent success in the active control group, was greater than the *a priori* specified margin of difference. Similar analyses were used for improvement in the individual assessment variables and the secondary variables. In addition, changes in Heart Insufficiency and Pulmonary Edema Scores, as well as changes in VHS and body weight were analyzed by mixed model analysis of variance.

d. Results of Effectiveness Assessments: Based on protocol compliance and individual case integrity, 268 cases (136 VETMEDIN, 132 active control) were included in the effectiveness data base. Within the effectiveness data base, the VETMEDIN and active control groups were similar at baseline. See Table 4.

Table 4: Effectiveness Data Base Characteristics at Baseline

Effectiveness Data Base VETMEDIN Group	**Effectiveness Data Base Active Control Group**
136 dogs Mean Body Wt. = 36.6 lb	132 dogs Mean Body Wt. = 37.6 lb
38.2% Class II HF 46.3% Class III HF 15.4% Class IV HF	31.8% Class II HF 44.7% Class III HF 23.5% Class IV HF
103 dogs had AVVI 33 dogs had DCM	101 dogs had AVVI 31 dogs had DCM
Of the 33 dogs with DCM: 9 had atrial fibrillation 18 were Doberman Pinschers	Of the 31 dogs with DCM: 4 had atrial fibrillation 12 were Doberman Pinschers

The results show that VETMEDIN was non-inferior to active control. See Table 5.

Table 5: Success Rates for Effectiveness Variables, by Treatment Group

	Success Rates[a] (% of Dogs)		
Variable (Versus Day 1)	**VETMEDIN**	**Active Control**	**Difference and Lower 95% Confidence Limit**
Treatment Success Day 29	80.7 SE[b] = 3.7 (n[b]=134)	76.3 SE = 4.0 (n=131)	4.5 SE = 5.1 L95%CL[c] = -3.9
Treatment Success Day 56	71.1 SE = 5.3 (n=113)	67.2 SE = 5.6 (n=110)	4.0 SE = 6.3 L95%CL = -6.3
Improvement in Heart Insufficiency Score by Day 8	87.5 SE = 4.1 (n=129)	83.5 SE = 4.9 (n=125)	4.0 SE = 4.4 L95%CL = -3.2
Improvement in Heart Insufficiency Score by Day 29	84.6 SE = 4.5 (n=122)	84.7 SE = 4.6 (n=115)	-0.1 SE = 4.6 L95%CL = -7.6
Improvement in Heart Insufficiency Score by Day 56	83.7 SE = 4.8 (n=110)	89.4 SE = 3.8 (n=98)	-5.6 SE = 4.7 L95%CL = -13.4
Improvement in Pulmonary Edema Score by Day 29	53.2 SE = 6.2 (n=119)	46.4 SE = 6.3 (n=114)	6.8 SE = 6.8 L95%CL = -4.4
Improvement in Pulmonary Edema Score by Day 56	53.0 SE = 5.7 (n=112)	41.1 SE = 5.9 (n=97)	11.9 SE = 7.0 L95%CL = 0.4
Improvement in OCE[d] Score by Day 29	97.7 SE = 1.5 (n=120)	96.0 SE = 2.1 (n=114)	1.6 SE = 2.3 L95%CL = -2.1
Improvement in OCE Score by Day 56	98.7 SE = 1.3 (n=77)	96.1 SE = 2.3 (n=75)	2.7 SE = 2.6 L95%CL = -1.6
Did **not** increase furosemide dosage ≥ 0.5 mg/kg by Day 29	78.3 SE = 4.4 (n=130)	68.6 SE = 5.2 (n=126)	9.8 SE = 5.6 L95%CL = 0.6

[a] The success rates represent the percent of dogs in each group showing treatment success or improvement. The success rates are back-calculated from the logit model least squares means.

[b] SE = Standard error of the percent, n = number of cases

[c] L95%CL = One-sided lower 95% confidence limit

[d] OCE = Overall Clinical Effectiveness

Of the 268 dogs evaluated for effectiveness, 2 of the VETMEDIN and 1 of the active control group dogs could not be evaluated for Treatment Success at Day 29 because of missing values for Pulmonary Edema (+/- OCE) Scores.

Table 6 provides the arithmetic means for Heart Insufficiency Score, Pulmonary Edema Score, Overall Clinical Effectiveness (OCE) Score, VHS, and body weight values by study day and treatment group for the effectiveness data base.

Table 6: Mean Results by Study Day for Effectiveness Data Base Cases

Mean Heart Insufficiency Score

	VETMEDIN	Active Control	Heart Insufficiency Score Definitions
Day 1	2.8 (n=136)	2.9 (n=132)	1 = modified NYHA Class I HF 2 = modified NYHA Class II HF 3 = modified NYHA Class III HF
Day 8	1.5 (n=129)	1.6 (n=125)	
Day 29	1.5 (n=122)	1.5 (n=115)	
Day 56	1.4 (n=110)	1.4 (n=98)	

Mean Pulmonary Edema Score

	VETMEDIN	Active Control	Pulmonary Edema Score Definitions
Day 1	2.7 (n=135)	2.5 (n=130)	1 = No pulmonary edema 2 = Mild interstitial density 3 = Moderate interstitial density
Day 29	1.9 (n=119)	1.9 (n=114)	
Day 56	1.9 (n=113)	2.0 (n=98)	

Mean Overall Clinical Effectiveness (OCE) Score

	VETMEDIN	Active Control	OCE Score Definitions
Day 29	1.8 (n=120)	1.7 (n=114)	With treatment, clinical condition: 1 = greatly improved 2 = moderately improved
Day 56	1.6 (n=77)	1.6 (n=75)	

Mean Vertebral Heart Size (VHS)

	VETMEDIN	Active Control	Comments
Day 1	12.05 (n=135)	12.06 (n=129)	The normal range for VHS is 8.5 to 10.5
Day 29	11.66 (n=119)	11.98 (n=114)	
Day 56	11.76 (n=113)	12.05 (n=98)	

Initial Mean Body Weight and Mean Weight Gain (lb)

	VETMEDIN	Active Control	Comments
Day 1	36.36 (n=136)	37.43 (n=132)	Day 1 -- initial mean weights
Day 8	-0.14 (n=130)	-0.68 (n=126)	Mean weight gain from Day 1 for the dogs remaining at each day. Negative values = weight loss.
Day 29	0.27 (n=121)	-0.90 (n=115)	
Day 56	0.66 (n=110)	-0.71 (n=100)	

Table 7 shows Treatment Success by treatment group and type of heart disease (AVVI or DCM) at Days 29 and 56.

Table 7: Treatment Success by Study Day, Treatment Group, and Type of Heart Disease (AVVI or DCM)

Study Day	**Number and % of Dogs with Treatment Success**			
	VETMEDIN		**Active Control**	
	AVVI	DCM	AVVI	DCM
Day 29	88 (n=101) 87.1%	20 (n=33) 60.6%	77 (n=100) 77.0%	23 (n=31) 74.2%
Day 56	66 (n=85) 77.6%	13 (n=28) 46.4%	56 (n=85) 65.9%	17 (n=25) 68.0%

e. Results of Safety Assessments: All dogs that received at least one dose of VETMEDIN (175 dogs) or active control (180 dogs) were evaluated for safety. The VETMEDIN group had the following prevalence (percent of dogs with at least one occurrence) of common adverse reactions/new clinical findings (not present in a dog prior to beginning study treatments): poor appetite (38%), lethargy (33%), diarrhea (30%), dyspnea (29%), azotemia (14%), weakness and ataxia (13%), pleural effusion (10%), syncope (9%), cough (7%), sudden death (6%), ascites (6%), and heart murmur (3%). Prevalence was similar in the active control group.

Adverse reactions/new clinical findings were seen in both treatment groups and were potentially related to CHF, the therapy of CHF, or both. The following adverse reactions/new clinical findings are listed according to body system and are not in order of prevalence: CHF death, sudden death, chordae tendineae rupture, left atrial tear, arrhythmias overall, tachycardia, syncope, weak pulses, irregular pulses, increased pulmonary edema, dyspnea, increased respiratory rate, coughing, gagging, pleural effusion, ascites, hepatic congestion, decreased appetite, vomiting, diarrhea, melena, weight loss, lethargy, depression, weakness, collapse, shaking, trembling, ataxia, seizures, restlessness, agitation, pruritus, increased water consumption, increased urination, urinary accidents, azotemia, dehydration, abnormal serum electrolyte, protein, and glucose values, mild increases in serum hepatic enzyme levels, and mildly decreased platelet counts.

Information relating to study mortality, arrhythmias, and other specific adverse reactions/new clinical findings is provided in the following pages.

1) Death: The VETMEDIN and active control groups overall had similar incidence of death due to congestive heart failure (CHF). Table 8 shows the study mortality by cause of death, treatment group, and type of heart disease (AVVI or DCM).

Table 8: Study Mortality, by Cause of Death, Treatment Group, and Type of Heart Disease (AVVI or DCM)

Cause of Death (Days 1 - 60) (includes euthanasia)	**Number and % of Dogs that Died**			
	VETMEDIN		**Active Control**	
	AVVI (n=126)	DCM (n=49)	AVVI (n=130)	DCM (n=50)
Progression of CHF (includes sudden death)	9 7.1%	16[a] 32.6%	16 12.3%	10 20%
Renal Failure[b]	0	0	3 2.3%	0
Neoplasia[b]	1 0.8%	0	0	0
GI[c] Disorders[b] (enteritis, GDV[c], intestinal ileus)	2 1.6%	2 4.1%	0	0
Other[b] (neck pain, CNS[d] disorder, trauma-coagulopathy)	1 0.8% neck pain case	0	1 0.8% CNS case	1 2.0% trauma case
Total Deaths by Type of Heart Disease	13 10.3%	18 36.7%	20 15.4%	11 22.0%
Total Deaths	31 17.7%		31 17.2%	
Total **CHF** Deaths	25 14.3%		26 14.4%	

[a] The 16 DCM dogs that died of CHF in the VETMEDIN group included one dog that was euthanized because of CHF and renal failure and another dog that was euthanized because of CHF and neoplasia.
[b] Dogs that died or were euthanized because of the development of renal failure or other non-CHF causes were not included in the effectiveness data base.
[c] GI = gastrointestinal, GDV = gastric dilatation-volvulus
[d] CNS = central nervous system

The VETMEDIN and active control groups had similar occurrence and dates of sudden death. Table 9 shows the numbers and percents of dogs with sudden death and the study dates at which sudden death occurred, by treatment group and type of heart disease (AVVI or DCM).

Table 9: Sudden Death, by Treatment Group, Type of Heart Disease (AVVI or DCM), and Day of Death

	VETMEDIN	**Active Control**
Dogs with AVVI that died of Sudden Death	5 (n=126) 4.0%	3 (n=130) 2.3%
Dates of Sudden Death of Dogs with AVVI	Days 1, 3, 4, 21, 60	Days 7, 16, 47
Dogs with DCM that died of Sudden Death	5 (n=49) 10.2%	6 (n=50) 12.0%
Dates of Sudden Death of Dogs with DCM	Days 19, 21, 27, 27, 44	Days 1, 3, 6, 7, 15, 35

2) Ruptured Chordae Tendineae and Left Atrial Tears: The VETMEDIN and active control groups had similar numbers of dogs (4 VETMEDIN, 4 active control) that had acute cardiac decompensation and death associated with ruptured chordae tendineae and/or left atrial tears confirmed by ultrasound (2 cases) or necropsy (6 cases).

3) Arrhythmias: Table 10 shows the number of dogs that had new (not present prior to beginning study medication) arrhythmias by type of arrhythmia, treatment group and type of heart disease. The VETMEDIN and active control groups had a similar occurrence of new arrhythmias overall.

Table 10: Number and Percent of Dogs with New Arrhythmias

Type of Arrhythmia	Number and % of Dogs			
	VETMEDIN		Active Control	
	AVVI (n=126)	DCM (n=49)	AVVI (n=130)	DCM (n=50)
Supraventricular Premature Contractions (Supraventricular extrasystoles, atrial bigeminy)	19 15.1%	4 8.2%	21 16.2%	5 10.0%
Supraventricular Tachycardia (Atrial, junctional, or sinus tachycardia)	11 8.7%	5 10.2%	15 11.5%	6 12.0%
Atrial Fibrillation	3 2.4%	5 10.2%	3 2.3%	2 4.0%
Bradyarrhythmia (First-degree AV[a] block, non-respiratory sinus arrhythmia, sinus bradycardia)	2 1.6%	0	5 3.8%	2 4.0%
Ventricular Premature Contractions	9 7.1%	5 10.2%	13 10.0%	6 12.0%
Ventricular Tachycardia	1 0.8%	3 6.1%	1 0.8%	1 2.0%
Bundle Branch Block (left or right)	0	2 4.1%	1 0.8%	0
Total dogs that developed new arrhythmias	45 35.7%	24 49.0%	59 45.4%	22 44.0%
Total dogs that developed new arrhythmias, by Treatment Group	69 39.4%		81 45.0%	

[a] AV = atrioventricular

4) Specific Adverse Reactions/New Clinical Findings:
Adverse reactions/new clinical findings (not present in a dog prior to beginning study treatments) reported only in the VETMEDIN group included: hemorrhagic gastroenteritis (1 dog), and gastric dilatation-volvulus (2 Doberman Pinschers on concurrent digoxin). The causal relationship of pimobendan to these findings is unknown.

Hemorrhagic gastroenteritis (with vomiting, hemorrhagic diarrhea, and increased hematocrit and total protein) developed on Day 19 in a Toy Poodle on VETMEDIN and furosemide. The dog responded to symptomatic treatment and completed the study.

Gastric dilatation-volvulus (GDV) occurred in 2 VETMEDIN group Doberman Pinschers on concurrent digoxin. One Doberman Pinscher developed GDV on Day 1, within 5 hours of her first doses of

VETMEDIN, furosemide, and digoxin, and was euthanized. Another Doberman Pinscher developed GDV on Day 14, responded to stomach tubing, and survived past Day 56 to die of CHF in the extended use study.

Renal Failure: The active control group had a greater percent of dogs that were euthanized or dropped out of the study because of renal failure. See Table 11.

Table 11: Study Deaths and Drop-outs Because of Renal Failure

	VETMEDIN (n=175)	**Active Control** (n=180)
Dogs euthanized because of renal failure	1 0.6%	3 1.7%
Dogs that dropped-out because of renal failure	1 0.6% (pyelonephritis)	5 2.8%
Totals and percents	2 1.1%	8 4.4%

Seizures: One dog from each treatment group was started on anticonvulsant therapy for seizures that occurred within the first week on study. Seizures were reported as agonal findings in dogs with end-stage CHF in both groups.

Decreased Platelet Counts: Mildly decreased platelet counts developed in 2 VETMEDIN group dogs with atrial fibrillation, 1 VETMEDIN group dog with ventricular tachycardia, and 1 active control group dog with atrial premature contractions. In contrast, 1 active control and 3 VETMEDIN group dogs with mild to moderately low platelet counts at baseline had improved platelet counts with time on the study.

Pruritus: Dogs in both treatment groups had pruritus as a new clinical finding; however, neither the investigators nor the owners of those dogs attributed the pruritus to VETMEDIN or active control therapy.

5) Concurrent Medication:
All but 4 VETMEDIN group and 2 active control group dogs received furosemide.

The concurrent use of digoxin did not increase mortality or the development of new arrhythmias in the VETMEDIN group compared to the active control group. Digoxin was allowed for the control of supraventricular tachyarrhythmias in any dog, but it was obligatory for active control group dogs with DCM. Table 12 shows the mortality and new arrhythmias that developed in dogs started on digoxin at the beginning of the study. To accurately compare the risk of digoxin use in

dogs with DCM between treatment groups, Table 12 shows the subset of DCM dogs that were started on digoxin because they had atrial fibrillation at baseline.

Table 12: Mortality and New Arrhythmias in Dogs on Concurrent Digoxin

Pertaining to Dogs started on Digoxin on Day 1	**Number and % of Dogs**	
	VETMEDIN	**Active Control**
Mortality in Dogs with AVVI	0 (n=6)	2 (n=13) 15%
Mortality in Dogs with DCM and Atrial Fibrillation	5 (n=14) 36%	4 (n=9) 44%
New Arrhythmias in Dogs with AVVI	2[a] (n=6) 33%	5[b] (n=13) 38%
New Arrhythmias in Dogs with DCM and Atrial Fibrillation	2[c] (n=14) 14%	1[c] (n=9) 11%

[a] 1 dog developed right bundle branch block, and 1 developed 1st degree AV block and atrial premature contractions

[b] 3 dogs developed ventricular premature contractions (VPCs), 1 developed atrial fibrillation, and 1 developed sinus tachycardia

[c] The dogs with DCM and atrial fibrillation on digoxin developed VPCs

In the small number of study dogs on β-blockers (usually atenolol), there was no difference in mortality between the VETMEDIN and active control groups. In this study, a β-blocker was only allowed as add-on therapy in cases where digoxin was not effectively controlling heart rate in supraventricular tachyarrhythmias. Four of the 8 VETMEDIN group dogs and 5 of the 10 active control group dogs that received a β-blocker died during the study.

Commonly used non-cardiovascular medications (used in at least 6 of the 175 of the dogs on VETMEDIN) included antiparasitic products (including heartworm preventative), topical ophthalmic and otic products, cephalexin, famotidine, levothyroxine sodium, amoxicillin-clavulanate, fluoroquinolones, metronidazole, and diphenhydramine.

f. Conclusions: The pivotal field study provides substantial evidence of the effectiveness of VETMEDIN (non-inferiority to enalapril maleate) for the management of the signs of mild, moderate, or severe (modified NYHA Class II, III, or IV) congestive heart failure in dogs due to AVVI or DCM, when used in combination with other appropriate congestive heart failure therapy. The pivotal field study also supports the safety of VETMEDIN in dogs with Class II, III, or IV CHF due to AVVI or DCM for a 2-month treatment period.

2. Extended Use Field Study

a. Title: Compassionate Use of VETMEDIN (pimobendan) in Dogs Suffering from Heart Failure due to Dilated Cardiomyopathy or Valvular Insufficiency, Study Number: 6150-0990-00C-088, (referred to as Study 088)

b. Investigators: A total of 21 of the 22 Pivotal Field Study (referred to as Study 087) sites enrolled dogs in this study. One site (Site 94) that participated in Study 087 did not continue participation in this extended use study because original enrollment was low. At Site 83, Dr. Sara Ford joined, and then replaced, Dr. Aaron Wey after he left the VCA Emergency Animal Hospital, San Diego, CA.

c. Study Design: Multi-site, open-label, field study

1) Objective: This study was designed to assess the incidence and nature of adverse reactions during a period of extended use of VETMEDIN in dogs that received VETMEDIN in Study 087.

2) Study Animals: Dogs from the VETMEDIN treatment group in Study 087 were eligible for Study 088. The study enrolled 137 client-owned dogs of various breeds, ranging in weight and age from 4.5 to 149.8 pounds and 1 to 16 years, respectively, on Day 1 of Study 087. Of the 137 dogs, 64 were male and 73 were female; 110 (80.3%) were diagnosed with AVVI and 27 (19.7%) were diagnosed with DCM. The seven most common breeds represented were mixed breed (25 dogs), Doberman Pinscher (12), Cocker Spaniel (12), Miniature/Toy Poodle (9), Maltese (8), Miniature Schnauzer (7), and Cavalier King Charles Spaniel (7).

3) Treatment Groups: Single Treatment Group, VETMEDIN

4) Drug Administration: VETMEDIN (pimobendan) was administered at 0.5 mg/kg per day, given in divided doses that were not necessarily equal, approximately 12 hours apart (morning and evening), using a suitable combination of 1.25, 2.5, and/or 5mg chewable tablets to achieve the 0.5 mg/kg daily dose.

Concurrent cardiac and non-cardiac medications were administered according to each investigator's clinical judgment.

5) Measurements and Observations:
Enrollment in Study 088 occurred on or soon after the day the dog completed Study 087. Procedures at enrollment and at each 3-month scheduled visit included recording potential adverse reactions, physical examination, body weight, heart murmur grade, Heart Insufficiency Score (modified NYHA Class of HF), characterization of arrhythmias, and clinical pathology. For each dog, study date in Study 088 was continued from Day 1 at the beginning of Study 087. Optional procedures included

chest radiographs and ECG. The primary variable was the recording of adverse reactions.

Owners were to observe their dogs daily for any problems and report them to the investigators, regardless of whether the problems were considered treatment-related or not. Dogs were rechecked at additional visits as needed for veterinary care.

6) Statistical Methods: Descriptive statistics and/or listings were provided for adverse reactions and new clinical findings, hematology, serum chemistry, Heart Insufficiency Score, days on study, and body weight.

d. Results of the Extended Use Field Study:
Of the 137 dogs enrolled in Study 088, 78 completed the study, 52 died or were euthanized, 5 were removed, and 2 dogs had final status unknown. Of the 110 AVVI and 27 DCM dogs enrolled in Study 088, 67 AVVI and 13 DCM dogs were on VETMEDIN therapy for more than 180 days, and 20 AVVI and 2 DCM dogs were on VETMEDIN therapy for more than 365 days. Dogs that completed Study 088 were on study (on VETMEDIN in Studies 087 and 088) ranging from 72 days to 727 days before the study ended. Dogs that died or were euthanized had a mean "days on study" of 224 and 174 days for dogs with AVVI and DCM, respectively, before death. The 5 dogs removed from the study included 1 dog that developed liver failure (removed Day 142), 1 dog due to gastrointestinal disease (Day 130), 1 owner withdrawal (Day 431), and 2 cases of poor owner compliance.

1) Death: Of the 52 dogs that died or were euthanized during Study 088, 38 (73%) died or were euthanized because of progressive CHF, including three dogs that were euthanized because of CHF and concurrent renal disease, failure, or azotemia. Three additional dogs were euthanized because of renal failure or azotemia. Eleven other dogs died or were euthanized because of deteriorating condition, poor quality of life, lymphoma, non-responsive incontinence, or other, unknown, or unspecified cause. Sudden death was reported in 7 of the 38 dogs that died of CHF, including 4 dogs with DCM (all Doberman Pinschers) and 3 dogs with AVVI (a Labrador Retriever, a Dalmatian, and a mixed breed dog).

2) Arrhythmias: Table 13 shows the number of dogs with new arrhythmias (i.e., not present in that particular dog in Study 087) in Study 088. The arrhythmias reported in Study 088 were consistent with the arrhythmias reported in Study 087.

Table 13: New Arrhythmias Detected in Study 088

Type of Arrhythmia	Number and % of Dogs[a] with New Arrhythmias in Study 088		
	AVVI + DCM (n=137)	AVVI (n=110)	DCM (n=27)
Supraventricular Premature Beats (Supraventricular extrasystoles, atrial bigeminy)	7 5.1%	5 4.5%	2 7.4%
Supraventricular Tachycardia (Atrial, junctional, sinus, or supraventricular tachycardia not otherwise classified)	3 2.2%	3 2.7%	0
Atrial Fibrillation	9 6.6%	6 5.4%	3 11.1%
Bradyarrhythmia (First-degree AV block, sinus bradycardia, sinus arrest)	4 2.9%	3 2.7%	1 3.7%
Ventricular Premature Beats	3 2.2%	2 1.8%	1 3.7%
Ventricular Tachycardia	3 2.2%	2 1.8%	1 3.7%

[a] A single dog may have had one or more types of new arrhythmias.

3) Adverse Reactions/New Clinical Findings:
The adverse reactions/new clinical findings reported in Study 088 were consistent with the adverse reactions/new clinical findings reported in Study 087, with the following exceptions:

Liver Failure and Elevated Liver-Associated Enzymes:
One dog on VETMEDIN and furosemide developed cholestatic liver failure on Day 140, with vomiting, anorexia, icterus, weight loss, increased serum bilirubin, alkaline phosphatase (AP) greater than 3 times (> 3X) the upper limit of normal (ULN), and alanine aminotransferase (ALT) > 7X ULN, with no evidence of neoplasia or infection on liver cytology. This dog had normal AP, ALT, and bilirubin values at baseline (prior to beginning treatment with VETMEDIN on Day 1 of Study 087).

Another dog (with normal values for AP and ALT at baseline) had elevated values of AP and ALT > 2X ULN on Day 264, which continued to increase to > 3X ULN on Day 354, when she was euthanized because of renal failure and CHF. She was on VETMEDIN, furosemide, and diethylstilbestrol up until Day 317, when enalapril maleate was added.

Azotemia and Renal Failure: Azotemia (defined as blood urea nitrogen (BUN) ≥ 50 and/or creatinine ≥ 2.5 mg/dL or by investigator designation) was identified as an adverse reaction/ new clinical finding in 16.1% of the 137 dogs during Study 088.

Of the 6 dogs on VETMEDIN that were euthanized because of renal failure, disease, or azotemia in Study 088, 4 dogs had received concurrent enalapril maleate (doses ranging from 0.5 to 1.8 mg/kg/day) and furosemide, and 2 dogs had only received concurrent furosemide. One of these 2 dogs was euthanized because of protein losing nephropathy and progression of CHF on Day 225, one week after he presented with vomiting and was found to have azotemia and hypoalbuminemia. This dog had normal hematology and clinical chemistry at baseline.

4) Survival in Doberman Pinschers with DCM: Twenty-three Doberman Pinschers with DCM enrolled in the VETMEDIN treatment group in Study 087. Ten died or were euthanized due to CHF or sudden death during Study 087. Eleven enrolled in Study 088. Six of the 11 DCM Doberman Pinschers in Study 088 were treated with VETMEDIN for more than 6 months, including one (a male with atrial fibrillation at Day 1) that was treated with VETMEDIN until sudden death on Day 542.

5) Concurrent Medications:
Concurrent Cardiovascular Medications: Furosemide was administered to all except 5 dogs (3 with AVVI and 2 with DCM) in Study 088. The most commonly used cardiovascular medications besides furosemide were enalapril maleate, digoxin, spironolactone, nitroglycerin, hydralazine, diltiazem, and atenolol. With the exception of nitroglycerin (an emergency drug), each of these drugs was administered concurrently with VETMEDIN for at least 1 month in at least 4 dogs. Nitroglycerin was used at least once in approximately 10% of the dogs in Study 088.

Adverse Reactions Associated with Concurrent Cardiovascular Medications: The addition of digoxin was associated with diarrhea and inappetence in one dog on VETMEDIN. The addition of digoxin and enalapril maleate was associated with vomiting in another dog on VETMEDIN. The addition of spironolactone was associated with diarrhea in another dog on VETMEDIN.

A dog that had collapsing episodes associated with the concurrent use of VETMEDIN and atenolol (plus furosemide and digoxin) in Study 087 did well on VETMEDIN, furosemide, digoxin, and diltiazem for the 4.5 months it was monitored under Study 088.

Concurrent Non-Cardiovascular Medications: The most commonly used non-cardiovascular medications in Study 088 (in at least 7 of the 137 dogs) included (roughly in the order of prevalence): antiparasitic products (including heartworm preventatives), metronidazole, theophylline, famotidine, hydrocodone, amoxicillin-clavulanate, diphenhydramine, fluoroquinolones, butorphanol, and metoclopramide. The addition of the bronchodilator theophylline (a phosphodiesterase inhibitor) was associated with decreased appetite, diarrhea, and vomiting in one dog on VETMEDIN.

e. Conclusions: The extended use field study provides evidence of the safety of VETMEDIN in dogs with mild, moderate, or severe (modified New York Heart Association (NYHA) Class II, III, or IV) congestive heart failure in dogs due to AVVI or DCM, when used in combination with other appropriate congestive heart failure therapy for periods of at least 6 months.

3. Palatability Study

a. Title: Acceptability of Flavored Pimobendan Chewable Tablets in Dogs

b. Study Director: Michael A Schnell, D.V.M., M.B.A., White Eagle Toxicology Laboratories, Doylestown, PA

c. Study Design: Palatability Study, open-label, single treatment group

1) This study was conducted in accordance with the Good Laboratory Practice Regulations (GLPs).

2) Study Animals: 20 female Beagles, 13 to 15 months of age, and 7.8 to 12.9 kg body weight. The dogs were given commercially available dog treats in their food bowls on Days -3 through -1 to acclimate them to receiving treats.

3) Treatment Groups: Single treatment group

4) Drug Administration: Each dog was offered one 2.5 mg VETMEDIN (pimobendan) chewable tablet 2 times per day (approximately 12 hours apart) for 14 days. Since the dogs weighed between 7.8 and 12.9 kg, they received doses of 0.32 to 0.19 mg/kg twice daily. Dogs were fasted for at least 2 hours prior to all treatments.

5) Measurements and Observations: At each offering, the chewable tablet was first placed in an empty food bowl. If it was not consumed within two minutes, it was offered by hand for another two minutes. The dogs were not to be coaxed into eating. Timing was done using a stopwatch. Consumption was recorded as to bowl, hand, or not consumed.

Other variables included physical examinations and body weights on Day -2, and twice daily clinical observations to assess behavior, respiratory character, fecal character, vomiting, and evidence of discomfort.

6) Statistical Methods: For acceptable palatability, at least 14 of the 20 dogs (70%) had to voluntarily consume at least 20 (70%) of the 28 tablets offered in an empty food bowl or by hand.

d. Results: Ninety percent (18 of 20 dogs) voluntarily consumed greater than 70% of the tablets offered. Including two dogs that consumed only 4 and 7% of the tablets offered, the average voluntary consumption was 84.2%.

e. Adverse Reactions: Clinical observations included 1 report of vomiting and 13 reports of soft stools or diarrhea occurring on or after the first day of dosing with VETMEDIN. None of the dogs needed veterinary care for these findings.

f. Conclusions: Palatability was acceptable. The observations of soft stools and diarrhea are consistent with observations in the target animal safety study and the field study.

III. TARGET ANIMAL SAFETY:

A. Laboratory Safety Studies

1. Four-Week IV Toxicity Study -- Dose Tolerance

a. Title: Subacute Toxicity Study with the Substance UD-CG 115 BS in Dogs after Intravenous Administration for Four Weeks, Study U85-0752

b. Investigators: R. Serbedija, A. Eckenfels, M. Bauer, H. Schneider; Boehringer Ingelheim Pharma KG, Biberach, Germany

c. Study Design: Laboratory toxicity study
1) This dose tolerance study was conducted in accordance with the Good Laboratory Practice Regulations (GLPs).

2) Study Animals: 30 healthy Beagles, 18 to 20 months of age, 8.4 to 15.0 kg body weight, 6 dogs per group (3 males and 3 females)

3) Treatment Groups and Drug Administration: See Table 14.

Table 14: Four-Week Toxicity Study Groups and Dosage Schedules

Dosage Group/ Daily Dosage	**Volume, Concentration, Frequency, Route of Administration, and Duration**	**Post-Treatment Recovery Time before Necropsy**
0 mg/kg/day Control	8.0 mL/kg of placebo IV[a] once daily for 4 weeks	none
0.5 mg/kg/day	1.0 mL/kg of 0.05% pimobendan IV once daily for 4 weeks	none
2.0 mg/kg/day	4.0 mL/kg of 0.05% pimobendan IV once daily for 4 weeks	none
8.0 mg/kg/day	8.0 mL/kg of 0.1% pimobendan IV once daily for 4 weeks	none
8.0 mg/kg/day	8.0 mL/kg of 0.1% pimobendan IV once daily for 4 weeks	7 wks

[a] Intravenous administration was accepted for dose tolerance testing due to greater bioavailability, and thus greater drug exposure, than with comparable dosages given via oral administration.

4) Measurements and Observations: mortality, morbidity, body weight, food consumption, ophthalmology, electrocardiography, hematology, clinical chemistry, urinalysis, necropsy, gross pathology, and histopathology

d. Results:

1) Electrocardiography: Dose dependent increases in heart rate were seen in the 2 mg/kg and 8 mg/kg dose groups after IV administration of pimobendan. In the 8 mg/kg group, heart rates were higher in the fourth week than in the first week of the study. One half hour after IV dosing in the fourth week, the mean heart rate of the 8 mg/kg group was 174 beats/min compared to 125 beats/min at baseline. The 2 and 8 mg/kg groups had shortened PQ and QT intervals, an expected physiological result of the increase in heart rate. ECG complexes were accentuated. Slight ST segment depression occurred in the 8 mg/kg group.

2) Cardiac Pathology/Histopathology: Lesions in the mitral valves, left ventricular outflow tract, and ventricular myocardium increased dose dependently in frequency and severity. Mitral valves had myxomatous thickening (described as nodular enlargements, mainly in the region of the rim of the valve and the ends of the chordae tendineae with granulation tissue and pads of mesenchymal tissue of varying degrees of vascularization in the atrium at the base of the valve). Left ventricular outflow tracts had endocardial thickening (described as hypercellular,

cushion-like endocardial swellings, partly pervaded with granulation tissue). The left ventricular papillary muscle, the septal myocardium, and parts of the right ventricular myocardium had isolated to multifocal small subendocardial foci of necrosis with scarring. See Table 15 for the incidence of cardiac lesions by group.

Table 15: Incidence of Cardiac Lesions after Four Weeks of IV Dosing

Abnormal Cardiac Pathology/Histopathology	**Incidence, in Dose Groups of 6 Dogs**			
	0 mg/kg	0.5 mg/kg	2.0 mg/kg	8.0 mg/kg at 4 wks
GROSS CARDIAC PATHOLOGY				
Increased mitral valve (MV) weight (MV weight > 300 mg)		1	1	3
MV thickened +/- small focal hemorrhages at the base of the MV		2	2	5
Thick and/or discolored attachment points of the chordae tendineae to the papillary muscle		1		4
Discolored left ventricle (LV) outflow tract endocardium		1	2	4
Macroscopic LV papillary muscle necrosis and/or scarring				2
Tricuspid valve blood cyst		1		
HISTOPATHOLOGY				
MV myxomatous thickening, moderate or marked		1	2	5
LV outflow tract endocardial thickening, moderate			1	3
Multifocal necrosis and/or scars of LV papillary, septal and/or right ventricle muscle (subendocardial ischemic lesions)			1	3
Hypertrophy of media of several LV intramural arteries				1

3) Hematology: Hemoglobin and erythrocyte counts were decreased (values less than the control group mean minus three standard deviations) in one dog in the 8 mg/kg group. Reticulocytes were increased in one 2 mg/kg and one 8 mg/kg group dog.

4) Clinical Chemistry: Serum alkaline phosphatase increased moderately (to < 3 times the upper limit of normal) in one of the six 0.5 mg/kg, two of the six 2 mg/kg, and three of the six 8 mg/kg group dogs. Livers were normal on histopathology.

5) Blood Glucose Curves: In blood glucose curves performed on the first day of dosing, blood glucose values increased shortly after the administration of IV pimobendan. In the 0.5 mg/kg group, the effects lasted about two hours and the maximum individual glucose value was 150 mg/dL [normal: 60 to 120 mg/dL]. In the 2.0 and 8.0 mg/kg groups, the duration of hyperglycemia was dose dependent and the maximum individual value was 191 mg/dL. In the fourth week of the study, elevations of blood glucose were only detected in the 8 mg/kg group.

e. Conclusions: Pimobendan administered IV daily to healthy Beagles caused dose dependent increases in heart rate, mitral valve myxomatous thickening, left ventricular outflow tract endocardial thickening, and ventricular muscle ischemic lesions (multifocal subendocardial necrosis and scarring). The cardiac pathology seen in these dogs is typical of positive inotropic drug toxicity in normal dog hearts, and is related to the physiologic effect of the drug on contractility and exaggerated hemodynamic response. Pimobendan administration was associated with moderate increases in serum alkaline phosphatase, transient elevations in blood glucose, individual decreases in hemoglobin and erythrocyte count, and individual increases in reticulocytes.

2. Six-Month Target Animal Safety Study

a. Title: VETMEDIN Target Animal Safety Study in Dogs,
Study BIVI 6150-0990-01C-074

b. Study Director: Michael A. Schnell, D.V.M., M.B.A., White Eagle Laboratories [Provident Preclinical, Inc.], Doylestown, PA

c. Study Design: Laboratory safety study, randomized and masked
1) This 6-month oral safety study was conducted in accordance with the Good Laboratory Practice Regulations (GLPs).

2) Study Animals: 24 healthy Beagles, 12 to 18 months of age and 8.7 to 15.3 kg body weight, 6 dogs per group (3 males and 3 females)

3) Treatment Groups and Drug Administration: See Table 16.

Table 16: Six-Month Target Animal Safety Study Groups and Dosages

Dosage Group	Total Daily Dosage, Doses per Day	Treatment Duration	Dosage Forms
0X	0 mg/kg/day, in 2 doses/day	180 days	Control: Identical to VETMEDIN tablets but without pimobendan
1X	0.5 mg/kg/day, in 2 doses/day	180 days	VETMEDIN: Chewable, scored tablets containing 1.25, 2.5 or 5.0 mg of pimobendan per tablet for oral administration
3X	1.5 mg/kg/day, in 2 doses/day	180 days	
5X	2.5 mg/kg/day, in 2 doses/day	180 days	

4) Measurements and Observations:
Clinical observations twice daily (including assessment of behavior, fecal character, vomiting, respiratory character, and evidence of discomfort)
Physical examinations at baseline and then every 4 weeks (including rectal temperature, heart and lung auscultations)
Body weights weekly
Food consumption sampled at baseline and then every 4 weeks
Hematology, clinical chemistry, and coagulation at baseline and on Days 2, 9, 16, 29, and Weeks 8, 13, 17, 21, and 26
Urinalyses at baseline and on Days 10, 17, 30, and Weeks 8, 13, 17, 21, and 26
Electrocardiography (by 24-hour Holter monitors) for heart rate and arrhythmias at baseline and at Weeks 4 and 20
Indirect blood pressure at baseline and then twice daily (pre-dosing and 2 hours post-dosing) on Days 1, 2 3, 7, 14, 28, and once daily (2 hours post-dosing) at Weeks 8, 13, 17, 21, and 26
Glucose curves at baseline, on Day 2, and then every 4 weeks
Ophthalmic examinations at baseline and at Weeks 13 and 26
Gross pathology and histopathology (with detailed cardiac pathology and histopathology)

5) Statistical Methods: Data obtained during the treatment period on each continuous variable measured at one time (organ weights and heart pathology parameters) were statistically evaluated using analysis of variance (ANOVA). Data on each continuous variable measured at more than one time (body weight, food consumption, ECG parameters, indirect blood pressure readings, hematology, serum chemistry, urinalysis parameters, blood glucose curve measures, and ECG parameters) were statistically evaluated via repeated-measures analysis of covariance. In the presence of a significant ($p \leq 0.10$) interaction of dose and time, Fisher's

least-significant-difference method (LSD; $p \leq 0.10$) was used to compare the 1X, 3X, and 5X group means to those of the control (0X) group at each measurement time. In the absence of a significant interaction effect, if the main effect of dose was significant ($p \leq 0.10$), Fisher's least-significant-difference method (LSD; $p \leq 0.10$) was used to compare the 1X, 3X, and 5X group means, averaged across all measurement times, to those of the control (0X) group, averaged across all measurement times. Incidences of ventricular premature contractions (VPCs) were analyzed by exact Jonkcheere-Terpstra tests for linear trend in dose.

d. Results:

1) Physical Examinations: Heart murmurs (grades II-III of VI) were detected on routine auscultation in one 3X dog (Day 65) and two 5X dogs (Days 135 and 163). The murmurs were not associated with clinical signs. On echocardiography, these three dogs had moderate to severe left ventricular hypertrophy, thickened mitral valves, and mitral valve insufficiency. Two of the three dogs had aortic outflow turbulence. On electrocardiograms, all three dogs had tall R waves (3.5 to 5.0 mV), and two of the three dogs had wide P waves (0.05 sec). Tall R waves are associated with increased left ventricular mass [normal: $\leq$ 2.5 to 3.0 mV]. Wide P waves are associated with left atrial enlargement [normal: $\leq$ 0.04 sec].

2) Electrocardiograph Results from 24-Hour Holter Monitoring:
Heart Rate: The mean heart rate was increased in the 5X group (101 beats/min) compared to the 0X group (94 beats/min). The group mean maximum heart rate was increased in the 5X (267 beats/min), 1X (257 beats/min), and 3X (252 beats/min) groups compared to the control group (240 beats/min).

Arrhythmias: No supraventricular premature complexes were recorded. Not counting escape beats, the 3X and 5X groups had slightly higher numbers of isolated ventricular ectopic complexes (VEs). The maximum number of non-escape VEs recorded either at baseline or in a control group dog was 4 VEs/24 hours. At baseline, 33% of the dogs had 1 to 4 non-escape VEs/24 hours. At weeks 4 or 20, 3/6 control dogs, 1/6 1X dogs, 6/6 3X dogs, and 4/6 5X dogs had at least 1 non-escape VE/24 hours. At either Week 4 or Week 20, three 3X group dogs had maximums of 33, 13, and 10 VEs/24 hours, and two 5X group dogs had maximums of 22 and 9 VEs/24 hours. One 1X group dog with no VEs at baseline had 6 VEs/24 hours at Week 4 and again at Week 20. None of the dogs had clinical signs associated with the VEs.

A 3X group dog had asymptomatic second-degree atrioventricular (AV) heart block on Holter recording at Weeks 4 and 20. This dog had a granulomatous lesion within the right atrial myocardium at necropsy. Asymptomatic second-degree AV heart block was also recorded in one 1X and one 5X dog at Week 20. No heart block was recorded at baseline or in the control group dogs.

3) Pathology/Histopathology: The heart was the only organ with treatment related findings on gross pathology or histopathology. The dogs that developed mitral insufficiency murmurs (one 3X and two 5X dogs) had myxomatous mitral valve thickening (a degenerative process characterized by subendothelial deposition of excessive mucopolysaccharide, collagen, and elastic tissue, which thickens and distorts the valve leaflets.) These three dogs had severe left ventricle and septal wall hypertrophy with multifocal subendocardial ischemic lesions. Left ventricular hypertrophy is attributed to the positive inotropic effect of pimobendan on the healthy heart. The multifocal subendocardial ischemic lesions (small focal areas of acute necrosis and fibrosis) are attributed to the inability of the vascular supply to meet the demands of the hypertrophied ventricle wall. The three dogs with murmurs also had left ventricular outflow tract endocardial thickening. Two of the three had left atrial endocardial thickening "jet lesions." The endocardial lesions are attributed to increased and turbulent blood flow.

   A granulomatous inflammatory lesion occurred within the right atrial myocardium of a 3X group dog. Right atrial granulomatous inflammatory lesions have been reported in canine toxicity studies of other potent vasodilators.[1] See Table 17 for the incidence of cardiac pathology by group. There was no evidence of congestive heart failure or ventricular dilation in any dog.

[1] Dogterom P, Zbinden G, Reznik G. Cardiotoxicity of vasodilators and positive inotropic/vasodilating drugs in dogs: an overview. Critical Reviews in Toxicology 1992; 22(3,4):217-224.

Table 17: Incidences of Cardiac Pathology by Group

Abnormal Cardiac Enlargement/Histopathology	**Number of Dogs (of 6) in Each Group [a]**			
	0X	1X	3X	5X
CARDIAC ENLARGEMENT				
Severe left ventricular hypertrophy, Increased[b] heart weight/body weight ratio, Increased left ventricle plus septal weight/body weight ratio, and Increased left ventricular free wall and interventricular septum thicknesses			1	2
Increased mitral valve weight				3
Increased left ventricular outflow tract thickness			2	3
Increased right ventricle weight/body weight ratio and atria weights/body weight ratio				1
HISTOPATHOLOGY				
Papillary muscle acute necrosis and scars in dogs with left ventricular hypertrophy (Multifocal subendocardial ischemic lesions)	1		1	2
Mitral valve myxomatous thickening, moderate to marked				3
Mitral valve myxomatous thickening, mild	1	1	3	
Chordae tendineae myxomatous thickening			1	2
Left ventricular outflow tract endocardial thickening		1	2	2
Left atrial endocardial thickening = jet lesion			1	1
Aortic intimal thickening			1	1
Granulomatous inflammatory lesion, 2x3x15 mm, within the right atrial myocardium			1	
Tricuspid valve myxomatous thickening, moderate.	3	1		
Tricuspid valve myxomatous thickening, mild			1	1
Tricuspid valve blood cyst			1	1

[a] Most of the pathological findings in the 3X and 5X groups occurred in the same three dogs.

[b] In this table, "increased" means that the result for that dog was greater than the 0X group mean plus two standard deviations.

4) Clinical Observations: The 5X and 1X groups had the most observations of soft and unformed stools, although the overall incidence was low (a maximum of 14 observations in one 5X group dog, with a total of 28 observations in the 5X group) and the diarrhea was self-limiting. The 0X group had the most vomiting, although the overall incidence was low and vomiting was self-limiting.

5) Hematology and Coagulation: Mean platelet counts were decreased in the 1X and 3X groups compared to the control group. However, all individual platelet counts were within the normal range.

   Pimobendan has been shown to inhibit platelet aggregation *in vitro*. There was no evidence of increased bleeding in the dogs in this study.

6) Clinical Chemistry: Mean serum potassium was increased in the 5X group compared to the control group. However, individual sample values for potassium remained within the normal range. Mean serum glucose was decreased in the 1X and 3X groups and increased in the 5X group compared to the control group, but all individual sample values for glucose were within the normal range. Three 1X dogs and one 5X dog had mildly elevated alkaline phosphatase values (< 2 times the upper limit of normal) in two to four of the nine blood samples taken during the study. Livers were normal on histopathology.

7) Glucose Curve: Serial blood glucose levels (before the morning dose and at 2, 4, and 6 hours post-dosing) were measured every 28 days during the study. The 5X group had a higher mean value (106 mg/dL) for maximum post-dose glucose compared to the control group (101 mg/dL). However, all individual sample values for glucose were within the normal range.

8) Indirect Blood Pressure: Mean systolic blood pressure at two hours post-dosing was lower for the 5X group (117 mmHg) compared to the control group (124 mmHg). Mean diastolic blood pressure was lower for the 3X group (74 mmHg) compared to the control group (82 mmHg). None of the dogs had clinical signs of hypotension. There was no measurable effect of treatment on blood pressure in the 1X group.

9) Other: No clinically relevant findings were reported for non-cardiac necropsy and histopathology, ophthalmology, body weights, food consumption, or other clinical pathology variables (hematology, coagulation, clinical chemistry, and urinalysis).

e. Conclusions: VETMEDIN administered to healthy Beagles at three and five times the recommended dose caused severe left ventricular hypertrophy with multifocal subendocardial ischemic lesions, myxomatous thickening of the mitral valves, mitral valve insufficiency murmurs, left atrial jet lesions, endocardial thickening of the left ventricular outflow tract, a granulomatous lesion within the right atrial myocardium, decreased blood pressure, increased heart rate, and a subtle increase in ventricular premature contractions. These effects are typical of positive inotropic and vasodilator drug toxicity in normal dogs. None of the dogs had clinical signs associated with their cardiac pathology. Infrequent and self-limiting diarrhea and vomiting, mild changes in blood glucose, mild increases in alkaline phosphatase and potassium, and a mild decrease in platelet count were associated with VETMEDIN administration but the effects were not dose dependent.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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:

> 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 Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that VETMEDIN, when used according to the label, is safe and effective for the management of the signs of mild, moderate, or severe (modified NYHA Class II[a], III[b], or IV[c]) congestive heart failure in dogs due to atrioventricular valvular insufficiency (AVVI) 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.

[a] A dog with modified New York Heart Association (NYHA) Class II heart failure has fatigue, shortness of breath, coughing, etc. apparent when ordinary exercise is exceeded.

[b] A dog with modified NYHA Class III heart failure is comfortable at rest, but exercise capacity is minimal.
[c] A dog with modified NYHA Class IV heart failure has no capacity for exercise and disabling clinical signs are present even at rest.

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 needed for diagnosis of modified NYHA Class II, III, or IV congestive heart failure in dogs due to atrioventricular valvular insufficiency or dilated cardiomyopathy, the selection of appropriate concurrent therapy, and monitoring the safe use of the product.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

U.S. Patent Number	Date of Expiration
5,364,646	November 15, 2011

VII. ATTACHMENTS:

Facsimile Labeling:
Package Insert
Bottle, Carton, and Shipper Labels for the 1.25 mg tablets
Bottle, Carton, and Shipper Labels for the 2.5 mg tablets
Bottle, Carton, and Shipper Labels for the 5 mg tablets

cc: Document Control Unit, for the administrative file of:
N-141273-Q-0001-OT
Courtesy copy for the sponsor
HFV-12, FOI Staff
HFA-305, Division of Dockets Management

Other administrative information: Not applicable

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