Date of Approval: February 13, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-575

Vetmedin® Solution

(pimobendan oral solution)

Dogs

Vetmedin® Solution (pimobendan oral solution) is indicated for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to clinical myxomatous mitral valve disease (MMVD) or dilated cardiomyopathy (DCM). Vetmedin® Solution 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 Animal Health USA, Inc.

Executive Summary

Vetmedin® Solution (pimobendan oral solution) is approved for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to clinical myxomatous mitral valve disease (MMVD) or dilated cardiomyopathy (DCM). Pimobendan is already approved under a different new animal drug application (NADA 141-273) as Vetmedin® chewable tablets for the same indication.

Vetmedin® Solution is an oral solution administered every 12 hours and comes with its own syringe calibrated for dosing based on the dog's weight.

Safety and Effectiveness

The sponsor conducted an *in vivo* bioequivalence study in young, healthy, male and female beagles comparing Vetmedin® Solution to Vetmedin® chewable tablets. The objective of the bioequivalence study was to provide a pharmacokinetic (PK) bridge for the safety and effectiveness of the already-approved chewable tablet formulation to the oral solution formulation.

On Days 0, 7, 14, and 21, all dogs received 5 mg of either Vetmedin® Solution or Vetmedin® chewable tablets. Blood samples were collected at multiple timepoints after each dose, and plasma samples were analyzed for concentrations of pimobendan and its metabolite for several PK parameters. No adverse reactions were reported.

Vetmedin® Solution met the criteria for bioequivalence for C_{max}, which is the maximum concentration, and $AUC_{0\text{-}t}$, which is the area under the curve from time zero to the last sampling time point. Therefore, the study provided a PK bridge for the safety and effectiveness of Vetmedin® chewable tablets to Vetmedin® Solution. The Freedom of Information Summary for the original approval of Vetmedin® chewable tablets, dated April 30, 2007, under NADA 141-273 contains a summary of the effectiveness and safety studies for dogs.

Conclusion

Based on the data submitted by the sponsor for the approval of Vetmedin® Solution, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-575

B. Sponsor

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

Drug Labeler Code: 000010

C. Proprietary Name

Vetmedin® Solution

D. Drug Product Established Name

pimobendan oral solution

E. Pharmacological Category

Inodilator (calcium sensitizer and phosphodiesterase III inhibitor)

F. Dosage Form

Solution

G. Amount of Active Ingredient

1.5 mg/mL

H. How Supplied

60 mL bottle containing 50 mL solution

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Vetmedin® Solution should be administered orally at a total daily dose of 0.23 mg/lb (0.5 mg/kg) body weight. The total daily dose should be divided into 2 equal portions administered approximately 12 hours apart (i.e., morning and evening). The syringe is calibrated to deliver the appropriate morning or evening dose when drawn to the dog's nearest weight in pounds. Vetmedin® Solution should be administered directly into the mouth. Do not mix into food.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

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

II. EFFECTIVENESS

The effectiveness of Vetmedin® Solution (pimobendan oral solution) for the management of the signs of mild, moderate, or severe congestive heart failure in dogs due to clinical myxomatous mitral valve disease (MMVD) or dilated cardiomyopathy (DCM), and for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis, was established by demonstrating bioequivalence with Vetmedin® (pimobendan) chewable tablets in the bioequivalence study summarized below. The effectiveness of Vetmedin® chewable tablets was evaluated in a field effectiveness study and an extended use field study. Please refer to the Freedom of Information (FOI) Summary for Vetmedin® chewable tablets for dogs (NADA 141-273), approved on April 30, 2007, for complete effectiveness information.

A. Dosage Characterization

The dose of Vetmedin® Solution is the same as that of Vetmedin® chewable tablets previously approved under NADA 141-273. Please refer to the FOI Summary for Vetmedin® chewable tablets, approved on April 30, 2007, for complete dosage characterization information.

B. Substantial Evidence

1. Bioequivalence Study

   Title: Bioequivalence Between Vetmedin® (pimobendan) 1.5 mg/mL Oral Solution and Vetmedin® (pimobendan) 5 mg Chewable Tablets in Dogs. (Study No. 2019163)

   Study Dates: April 2021 to March 2022

   Study Location: Walsrode, Germany

Study Design:

Objective: The study objective was to demonstrate the bioequivalence between the Test article, Vetmedin® Solution, and the Reference article, Vetmedin® chewable tablets.

Study Animals: Twenty-four male and female, adult Beagle dogs (12 male/12 female) with a body weight range of 9.0 to 16.5 kg (determined on Day -1) were enrolled in this study. Animals were randomly allocated to two groups, 12 animals per group.

Experimental Design: This study was conducted in compliance with good laboratory practice (GLP) regulations. The study was designed as a randomized (blocked by weight), masked, four-period, two-sequence, single-dose, full replicative cross-over design (Table II.1).

Table II.1. Treatment Groups.

Group Number	No. of Animals	Target Dose (mg/animal)[1]	Route	Treatment[2] Study Day 0	Treatment[2] Study Day 7	Treatment[2] Study Day 14	Treatment[2] Study Day 21
I	12	5	Oral	A	B	A	B
II	12	5	Oral	B	A	B	A

[1] mg pimobendan/animal (administered once each treatment day)
[2] A = Vetmedin® Solution, 1.5 mg pimobendan/mL (Test article)
B = Vetmedin® chewable tablets, 5 mg pimobendan/tablet (Reference article)

Drug Administration: In the four treatment periods (on Days 0, 7, 14, and 21) either Vetmedin® Solution or Vetmedin® chewable tablets was administered by single oral administration at a total targeted dose of 5 mg pimobendan/animal.

Measurements and Observations: Blood samples were drawn shortly prior to treatment and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours after each treatment. Clinical observations were conducted at these time points.

Pharmacokinetic (PK) Analysis: Plasma samples were analyzed for concentrations of the active ingredient (parent compound) pimobendan and its metabolite using a validated liquid chromatography with tandem mass spectrometry detection (LC/MS/MS) method. The lower limit of quantification (LLOQ) was 0.100 ng/mL for both compounds. Values below LLOQ occurring before the first quantifiable concentration were set to zero. The first value below the LLOQ that occurred after C_{max}, and all subsequent values, irrespective of whether they were below the LLOQ or not, were set to missing.

Plasma concentration data were subjected to noncompartmental PK analysis using nominal sampling times. Estimates of the PK variables maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve from the time of dosing to the last quantifiable concentration (AUC_{last}), and area under the curve from the time of dosing extrapolated to infinity ($AUC_{0-\infty}$) were made for each animal, individually, in each period. The AUC was determined via

linear trapezoidal summation. $AUC_{0-\infty}$ and half-life ($t_{½}$) were calculated by log-linear regression analysis of the terminal phase of plasma concentration-time data using at least three data points.

Statistical Methods: Prior to the bioequivalence analysis, C_{max} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (S_{WR}) of the Reference article was calculated separately for transformed C_{max} and AUC.

The S_{WR} was greater than 0.294 for C_{max} and AUC, so the Reference Scaled Average Bioequivalence (RSABE) method was used, and bioequivalence was established based on the following two criteria:

- The estimated 95% upper confidence bound for $(\mu_T-\mu_R)^2- \theta^*\sigma^2_{WR}$ is less than zero (0), where μ_T and μ_R are the population means of the natural log transformed primary variable for the Test and Reference articles, respectively, $\theta = (\ln (1.25)/\sigma_{W0})^2$ and $\sigma_{W0} = 0.25$.
- The point estimate of the geometric mean ratio (GMR) is between 0.8 to 1.25.

Results: The PK parameters are summarized in Table II.2.

Table II.2. Summary Statistics of the Plasma Pimobendan PK Parameter Estimates.

Parameter	Treatment	No. observations†	Means‡	90% Confidence interval‡		Minimum	Maximum
AUC_{last} (h*ng/mL)	Vetmedin® Solution	48	31.4	26.6	37.2	3.00	157
	Vetmedin® chewable tablets	48	36.8	31.3	43.3	10.7	236
$AUC_{0-\infty}$ (h*ng/mL)	Vetmedin® Solution	47	31.6	26.7	37.4	3.13	157
	Vetmedin® chewable tablets	48	37.0	31.5	43.5	10.8	236
C_{max} (ng/mL)	Vetmedin® Solution	48	17.6	14.3	21.7	2.38	90.6
	Vetmedin® chewable tablets	48	19.0	15.5	23.3	2.99	110
$t_{1/2}$ (h)	Vetmedin® Solution	47	0.815	0.742	0.895	0.410	1.72
	Vetmedin® chewable tablets	48	0.733	0.665	0.809	0.392	3.23
T_{max} (h)	Vetmedin® Solution	48	0.750	-	-	0.250	3.00
	Vetmedin® chewable tablets	48	1.00	-	-	0.500	5.00

†Twenty-four dogs were used. Each dog received Vetmedin® Solution twice and Vetmedin® chewable tablets twice. In one dog, there were insufficient data points to determine $t_{½}$ and $AUC_{0-\infty}$.

‡For AUCs, C_{max}, and $t_{½}$, the geometric means and the associated confidence interval are presented; for T_{max} the median and associated minimum and maximum values are presented.

With respect to pimobendan, the within-subject standard deviation, S_{WR}, of the Reference article was 0.601 for C_{max} and 0.417 for AUC_{last}. Because the S_{WR} was ≥ 0.294 for both parameters, only the RSABE method was used for determination of equivalence as mentioned above. The critical bounds were -0.153 for C_{max} and -0.029 for AUC_{last} (Table II.3).

The point estimates were 0.927 for C_{max} and 0.853 for AUC_{last} and were contained within the 0.80 - 1.25 acceptance limit.

Table II.3. Summary Statistics Using the Reference-scaled Average Bioequivalence Approach.

Parameter	S_{WR}	Ratio◊	95% Upper Bound$
AUC_{last}	0.417	0.853	-0.029
C_{max}	0.601	0.927	-0.153

◊ Ratio = Vetmedin® Solution / Vetmedin® chewable tablets.
$ 95% upper confidence bound for (μT-μR) 2- θ*σ2WR.

The results demonstrated that Vetmedin® Solution is bioequivalent to Vetmedin® chewable tablets at a targeted dose of 5 mg pimobendan/animal.

The bioequivalence study also demonstrated similar AUC and C_{max} of the active metabolite between Vetmedin® Solution and Vetmedin® chewable tablets.

Adverse Reactions: No treatment-related adverse reactions were noted during this study and no concurrent medications were administered.

Conclusions: For C_{max} and AUC_{last}, the point estimates were within the acceptance limit (0.80, 1.25) and the 95% upper confidence bounds were ≤ 0. Bioequivalence was established between Vetmedin® Solution and Vetmedin® chewable tablets in dogs providing a bridge to effectiveness and safety studies performed with Vetmedin® chewable tablets for dogs (NADA 141-273).

III. TARGET ANIMAL SAFETY

The safety of Vetmedin® Solution (pimobendan oral solution) was established by demonstrating bioequivalence with Vetmedin® (pimobendan) chewable tablets in the bioequivalence study summarized in section II.B.1. The safety of Vetmedin® chewable tablets was demonstrated in two laboratory safety studies. Please refer to the FOI Summary for Vetmedin® chewable tablets for dogs (NADA 141-273), approved on April 30, 2007, for complete safety information.

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® Solution:

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.

Wash hands after use. This product may cause eye irritation. Avoid contact with eyes. In case of contact, flush affected eye(s) immediately and thoroughly with water. If wearing contact lenses, flush the eyes first with water and then remove the lens(es) and continue to flush thoroughly with water. If eye irritation continues, seek medical advice and provide this product information to the physician.

Exposure to product may induce a local or systemic allergic reaction in sensitized individuals.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Vetmedin® Solution, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

A. Marketing Status

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 congestive heart failure and monitor for treatment effect and potential adverse reactions.

B. Exclusivity

Vetmedin® Solution, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C Act.

C. Patent Information

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