Date of Approval: April 25, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-728

Pimomedin™

(pimobendan)

Chewable tablet

Dogs

Pimomedin™ (pimobendan) 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). Pimomedin™ 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:

Cronus Pharma Specialities India Private Ltd.

Executive Summary

Pimomedin™ (pimobendan) chewable tablets 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). Pimomedin™ is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis in dogs. Pimomedin™ is a generic version of Vetmedin®.

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Pimomedin™	pimobendan	Abbreviated New Animal Drug Application (ANADA) 200-728	Cronus Pharma Specialities India Private Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	Vetmedin®	pimobendan	New Animal Drug Application (NADA) 141-273	Boehringer Ingelheim Animal Health USA, Inc.

Pimobendan is a non-sympathomimetic, non-glycoside inotropic drug. Pimobendan stimulates the heart by increasing calcium sensitivity of cardiac muscle cells and by inhibiting the activity of type III phosphodiesterase (PDE3), resulting in vasodilation.

Bioequivalence

The Federal Food, Drug, and Cosmetic (FD&C) Act allows an animal drug sponsor to submit an abbreviated new animal drug application (ANADA) for a generic version of an approved brand name animal drug (also called the reference listed new animal drug or RLNAD). This law typically requires the sponsor to show that the generic drug is bioequivalent to the approved RLNAD. Broadly, bioequivalence means the generic drug is absorbed by and performs the same way in the animal's body as the RLNAD, which has already been shown to be safe and effective when used according to the label. The FD&C Act doesn't require the sponsor to submit new effectiveness or target animal safety data in the ANADA for a generic animal drug.

The sponsor conducted one *in vivo* blood-level study in 40 healthy, fasted dogs to show that the 5 mg Pimomedin™ chewable tablets are bioequivalent to the 5 mg Vetmedin® chewable tablets. No serious adverse events were reported during the study.

Vetmedin® is available in 1.25 mg, 2.5 mg, 5 mg, and 10 mg chewable tablets. The sponsor conducted comparative *in vitro* dissolution studies comparing the dissolution profile of the 1.25 mg, 2.5 mg, and 10 mg generic tablets. The 5 mg generic chewable tablet was used as the comparator because it was shown to be bioequivalent to the 5 mg Vetmedin® chewable tablet in the *in vivo* blood-level study. The dissolution data demonstrated that the generic 1.25 mg, 2.5 mg, and 10 mg pimobendan chewable tablets are comparable to the generic 5 mg tablet strength. Therefore, the 1.25 mg, 2.5 mg and 10 mg generic chewable tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver), and FDA granted a biowaiver for this strength.

Conclusions
Based on the data submitted by the sponsor for the approval of Pimomedin™, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-728

B. Sponsor

Cronus Pharma Specialities India Private Ltd.
Plot No.9(B), Survey No. 99/1, GMR Hyderabad Aviation SEZ Ltd
Mamidipalle Village, Balapur Mandal, Shamshabad, Rangareddy,
Hyderabad, Telangana, 500108, India

Drug Labeler Code: 069043

C. Proprietary Name

Pimomedin™

D. Drug Product Established Name

pimobendan

E. Pharmacological Category

Inodilator

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

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

H. How Supplied

Available as 1.25, 2.5, 5 and 10 mg oblong half-scored chewable tablets – 50 tablets per bottle

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Pimomedin™ 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

Pimomedin™ (pimobendan) 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). Pimomedin™ is indicated for use with concurrent therapy for congestive heart failure (e.g., furosemide, etc.) as appropriate on a case-by-case basis.

N. Reference Listed New Animal Drug

Vetmedin®; pimobendan; NADA 141-273; Boehringer Ingelheim Animal Health USA, Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD pimobendan 5 mg chewable tablet. The RLNAD is available in 1.25 mg, 2.5 mg, 5 mg, and 10 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 40 healthy, fasted dogs. The pivotal parameters to evaluate bioequivalence are the observed maximum plasma drug concentration (C_{MAX}) and area under the concentration-time curve (AUC) from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX}. Bioequivalence was demonstrated between the 5 mg RLNAD and the 5 mg generic tablets by the average bioequivalence approach as described in the Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 1.25 mg, 2.5 mg, and 10 mg chewable tablets was requested. Dissolution data was used to demonstrate that the generic 1.25 mg, 2.5 mg, and 10 mg pimobendan chewable tablets are comparable to the generic 5 mg chewable tablets strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 1.25 mg, 2.5 mg, and 10 mg pimobendan chewable tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: A Plasma Bioavailability Study of test article Pimobendan Chewable Tablets 5 mg and reference article Vetmedin® (pimobendan) Chewable Tablets 5 mg administered orally in dogs. (Study No. 19277)

Study Dates: January 21, 2020 to September 26, 2020

Study Locations:

In-life phase: Telangana State, India

Bioanalytical testing: Andhra Pradesh, India

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 5 mg pimobendan and the RLNAD in fasted dogs.

Study Animals: 40 intact male beagle dogs, 1-5 years of age

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 5 mg of either the generic or RLNAD pimobendan according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of pimobendan were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Method:

The laboratory study was conducted as a randomized, masked two-period, two-sequence, two-treatment, single-dose crossover design using 40 dogs with a 7-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

A mixed-effect model was used to evaluate bioequivalence. The model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90% confidence interval for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC are contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below, C_{MAX} and AUC fall within the prescribed bounds (Table II.1). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation

Parameter	Generic Mean	RLNAD Mean	Ratio◊	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	15.56†	15.05†	1.03	0.89	1.21
C_{MAX} (ng/mL)	16.46†	16.33†	1.01	0.84	1.22
T_{MAX} (hours) (SD)‡	0.64 (0.37)‡	0.72 (0.43)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 5 mg pimobendan and the RLNAD are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 5 mg pimobendan strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 1.25 mg, 2.5 mg, and 10 mg chewable tablets was requested. To qualify for a biowaiver for each of these product strengths, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic 1.25 mg, 2.5 mg, and 10 mg pimobendan chewable tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons for the 10 mg strength. Comparisons were made between the following tablets:

- Generic 5 mg and generic 1.25 mg tablets
- Generic 5 mg and generic 2.5 mg tablets
- Generic 5 mg and generic 10 mg tablets

The objective was to satisfy f_2 criteria between the generic 5 mg chewable tablets strength and the generic 1.25 mg, 2.5 mg, and 10 mg chewable tablets strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.1N Hydrochloric acid
- Dissolution medium volume: 900 mL
- Temperature: 37 °C ± 0.5 °C
- Paddle speed: 50 rpm

- Number of vessels: 12
- Data points: 5, 15, 20, 30, 45, and 60 minutes

The generic drug lot number used in the *in vivo* bioequivalence study was the same lot used to support the *in vitro* profile comparisons. Analytical method validation was required to ensure that the quantification of drug concentrations in all samples was accurate and precise.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. The percent coefficient of variation for all generic product profiles was within acceptable limits. Only one measurement should be considered after 85% dissolution of one of the products. The f_2 should be greater than 50 to ensure sameness or equivalence of two profiles.

CVM estimated f_2 metrics based on mean data, and a summary of the results is presented in table II.2 below:

Table II.2. Similarity Results

Dissolution Comparison	Similarity Results
5 mg generic to the 1.25 mg generic	> 85% dissolved within 15 minutes supports sameness, f_2 not required
5 mg generic to the 2.5 mg generic	> 85% dissolved within 15 minutes supports sameness, f_2 not required
5 mg generic to the 10 mg generic	50.1

Study results demonstrate similar dissolution profiles for all comparisons. However, because of rapid dissolving characteristics (> 85% in 15 minutes) in the 1.25, 2.5, and 5 mg strengths, a dissolution profile comparison using the f_2 test is unnecessary. The calculated f_2 value is ≥ 50 for the 5 mg versus 10 mg strength chewable tablets, indicating sameness. When comparative profiles between tablets do not require an f_2 test because of rapid dissolution or when the f_2 value is ≥ 50, the product strengths used in the comparison qualify for a biowaiver. Therefore, a biowaiver for the generic 1.25 mg, 2.5 mg, and 10 mg pimobendan chewable tablets is granted.

III. 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 ANADA.

IV. USER SAFETY

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

User Safety Warnings: 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.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Pimomedin™, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.