Date of Approval: March 31, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-747

Maropitant Citrate

Tablets

Dogs

Maropitant Citrate tablets are indicated for the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs.

Sponsored by:

ZyVet Animal Health Inc.

Executive Summary

Maropitant Citrate tablets are approved for the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs. The reference listed new animal drug (RLNAD) is Cerenia® tablets sponsored by Zoetis Inc. under NADA 141-262. This is the first generic maropitant citrate tablets for dogs.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 60 mg Maropitant Citrate tablet is bioequivalent to the 60 mg Cerenia® tablet. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strengths. Based on the dissolution data, the 16, 24, and 160 mg tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). FDA granted a biowaiver for these strengths.

Conclusions

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

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I. GENERAL INFORMATION

A. File Number

ANADA 200-747

B. Sponsor

ZyVet Animal Health Inc.
73 Route 31N
Pennington, NJ 08534

Drug Labeler Code: 086117

C. Proprietary Name

Maropitant Citrate

D. Drug Product Established Name

maropitant citrate

E. Pharmacological Category

Antiemetic

F. Dosage Form

Tablet

G. Amount of Active Ingredient

16, 24, 60, or 160 mg of maropitant as maropitant citrate per tablet

H. How Supplied

Each tablet strength is scored and packaged in blister packs containing 4 tablets per perforated sheet.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

For Prevention of Acute Vomiting in dogs 2 -7 months of age: Administer Maropitant Citrate tablets orally at a minimum dose of 2 mg/kg (0.9 mg/lb) body weight once daily for up to 5 consecutive days.

For Prevention of Acute Vomiting in dogs 7 months of age and older: Administer Maropitant Citrate tablets orally at a minimum dose of 2 mg/kg (0.9 mg/lb) body weight once daily until resolution of acute vomiting.

For Prevention of Vomiting due to motion sickness in dogs 4 months of age and older: Administer Maropitant Citrate tablets orally at a minimum dose of 8 mg/kg (3.6 mg/lb) body weight once daily for up to 2 consecutive days.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Maropitant Citrate tablets are indicated for the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs.

N. Reference Listed New Animal Drug (RLNAD)

Cerenia®; maropitant citrate; NADA 141-262; Zoetis 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 in dogs to demonstrate product bioequivalence using the generic and RLNAD maropitant citrate 60 mg tablets. The RLNAD is available in 16 mg, 24 mg, 60 mg, and 160 mg tablet sizes. The *in vivo* blood-level study was conducted in 28 healthy, fed 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 60 mg RLNAD maropitant citrate tablets and the 60 mg generic maropitant citrate 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 16 mg, 24 mg, and 160 mg tablets was requested. Dissolution data was used to demonstrate that the generic 16 mg, 24 mg, and 160 mg maropitant citrate tablets are comparable to the generic 60 mg tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 16 mg, 24 mg, and 160 mg maropitant citrate tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: A Masked, Randomized, Four Period, Two Sequence, Single Dose Oral, Replicate Cross Over Bioequivalence Study of Maropitant Citrate Tablets (60 mg) and Cerenia® Tablets (60 mg) in Healthy Dogs under Fed Conditions. (Study No. 113-BC-2820)

Study Dates: August 31, 2021, to March 10, 2022

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Ontario, Canada

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 60 mg Maropitant Citrate tablets and the RLNAD 60 mg Cerenia® (maropitant citrate) tablets in fed dogs.

Study Animals: 28 intact male and female dogs weighing 7.5 to 8.8 kg on study day -5 and between 282 and 849 days old on study day 0.

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

Drug Administration: Each animal received 60 mg of either the generic or RLNAD maropitant citrate according to their randomized treatment sequence (generic/RLNAD/generic/RLNAD or RLNAD/generic/RLNAD/generic).

Measurements and Observations: The plasma concentrations of maropitant 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 Methods:

The laboratory study was conducted as a randomized, masked, four-period, two-sequence, two-treatment, single-dose crossover design using 28 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.

The mixed reference-scaled average bioequivalence approach was used to evaluate bioequivalence. Prior to the analysis, C_{MAX} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (s_{WR}) of the RLNAD was calculated separately for transformed C_{MAX} and AUC to select the appropriate analysis approach based on FDA guidances. The s_{WR} was less than 0.294 for both

C_{MAX} and AUC, so the average bioequivalence method was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Period was modeled as a repeated factor. Bioequivalence was established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratio (generic:RLNAD) of both C_{MAX} and AUC were contained within the acceptance limits of 0.80 to 1.25.

Results:

As seen in the table below (Table II.1), C_{MAX} and AUC fall within the prescribed bounds. 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	8856.4	8669.7	1.02	1.00	1.05
C_{MAX} (ng/mL)	781.3	779.6	1.00	0.97	1.04
T_{MAX} (hours) (SD)‡	1.86 (0.64)‡	1.71 (0.55)‡	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 60 mg Maropitant Citrate tablets and the RLNAD 60 mg Cerenia® (maropitant citrate) tablets are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood level bioequivalence study was conducted using the 60 mg maropitant citrate tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 16 mg, 24 mg and 160 mg 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 16 mg, 24 mg, and 160 mg tablets. Comparisons were made between the following tablets:

- Generic 60 mg tablets and the RLNAD 60 mg tablets
- Generic 60 mg tablets and the Generic 16 mg tablets
- Generic 60 mg tablets and the Generic 24 mg tablets
- Generic 60 mg tablets and the Generic 160 mg tablets

The objective was to satisfy f_2 criteria between the generic tablet strengths to the corresponding RLNAD tablet strengths. The analytical method and dissolution conditions were determined to be adequately validated.

Test conditions were as follows:

- Dissolution apparatus: USP Method 2 (paddles)
- Dissolution medium: 0.1N HCL.
- Dissolution medium volume: 900 mL
- Temperature: 37 °C + 0.5 °C
- Paddle speed: 75 rpm
- Number of vessels: 12
- Data points: 5, 10, 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.

All tablet strengths demonstrated ≥ 85% dissolution in less than 15 minutes. Study results demonstrate similar dissolution profiles for all comparisons. Because rapid dissolution was demonstrated (> 85% in 15 minutes) in all strengths, a dissolution profile comparison using the f_2 test is unnecessary. 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 16 mg, 24 mg, and 160 mg (maropitant citrate) tablets was 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 Maropitant Citrate:

Not for use in humans. Keep out of the reach of children. In case of accidental ingestion, seek medical advice. Topical exposure may elicit localized allergic skin reactions in some individuals. Repeated or prolonged exposure may lead to skin sensitization. Wash hands with soap and water after administering drug. Maropitant Citrate is also an ocular irritant. In case of accidental eye exposure, flush with water for 15 minutes and seek medical attention.

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 Maropitant Citrate, when used according to the label, is safe and effective for the indications listed in Section I.M. above.