Date of Approval: February 2, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-739

Carprofen

Chewable tablets

Dogs

Carprofen is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

Sponsored by:

ZYVET AH, Inc.

Executive Summary

Carprofen chewable tablets are approved for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs. The reference listed new animal drug (RLNAD) is RIMADYL® (carprofen) chewable tablets sponsored by Zoetis Inc. under NADA 141-111.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 25 mg Carprofen is bioequivalent to the 25 mg RIMADYL®. 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 75 mg and 100 mg chewable 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 Carprofen, 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 200-739

B. Sponsor

ZYVET AH, Inc.
73 Route 31N
Pennington, NJ 08534

Drug Labeler Code: 086117

C. Proprietary Name

Carprofen

D. Drug Product Established Name

carprofen

E. Pharmacological Category

Non-steroidal anti-inflammatory drug

F. Dosage Form

chewable tablet

G. Amount of Active Ingredient

25 mg, 75 mg and 100 mg of carprofen per tablet

H. How Supplied

Each tablet size is scored and packaged in bottles containing 30, 60 or 180 tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The recommended dosage for oral administration to dogs is 2 mg/lb of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight once daily or divided and administered as 1 mg/lb twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. Carprofen chewable tablets are scored and dosage should be calculated in half-tablet increments.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Carprofen is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

N. Reference Listed New Animal Drug

RIMADYL®; carprofen; NADA 141-111; 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 to demonstrate product bioequivalence using the generic and RLNAD carprofen 25 mg chewable tablets. The RLNAD is available in 25, 75, and 100 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 34 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 25 mg RIMADYL® (carprofen) chewable tablets and the 25 mg generic Carprofen chewable 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 75 mg and 100 mg chewable tablets was requested. Dissolution data was used to demonstrate that the generic 75 mg and 100 mg carprofen chewable tablets are comparable to the generic 25 mg chewable tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 75 mg and 100 mg carprofen chewable tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: A Masked, Balanced, Randomized, Two Period, Two Sequence, Single Oral Dose, Crossover Bio-Equivalence Study of Carprofen Chewable Tablet 25 mg and Rimadyl® Chewable Tablet 25 mg in Healthy Adult Beagle Dogs under Fasting Conditions. (Study No. 20235620)

Study Dates: June 23, 2021 to January 12, 2022

Study Locations:

In-life phase: North Brabant, The Netherlands

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 25 mg Carprofen chewable tablet and the RLNAD 25 mg RIMADYL® (carprofen) chewable tablet in fasted dogs.

Study Animals: 34 intact male beagle dogs, between 8 months and 3 years of age and weighing between 6.81 and 12.00 kg.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Organization for Economic Cooperation and Development Principles of Good Laboratory Practice.

Drug Administration: Each animal received 25 mg of either the generic or RLNAD carprofen according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of carprofen 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 34 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 and room. 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 (ug/mL)*hour	152.1†	154.5†	0.98	0.95	1.02
C_{MAX} (ug/mL)	22.3†	24.5†	0.91	0.86	0.96
T_{MAX} (hours) (SD)‡	1.16 (0.52)‡	0.98 (0.37)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic/RLNAD
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 25 mg Carprofen chewable tablets and the RLNAD 25 mg RIMADYL® (carprofen) chewable tablets are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg carprofen chewable tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 75 mg and 100 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 25 mg, 75 mg, and 100 mg carprofen chewable tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 25 mg and generic 75 mg chewable tablets
- Generic 25 mg and generic 100 mg chewable tablets

The objective was to satisfy the f_2 criteria between the generic 25 mg chewable tablet strength and the generic 75 mg and 100 mg carprofen chewable tablets.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II with sinker

- Dissolution medium: 0.05 M Phosphate buffer, pH 7.5
- Dissolution medium volume: 900 mL
- Temperature: 37 °C ± 0.5 °C
- Paddle speed: 100 rpm
- Number of vessels: 12
- Data points: 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.

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 similarity factor (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
25 mg generic to the 75 mg generic	71.6
25 mg generic to the 100 mg generic	78.9

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 75 mg and 100 mg carprofen 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 Carprofen:

Keep out of reach of children. Not for human use. Consult a physician in cases 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 Carprofen, when used according to the label, is safe and effective for the indications listed in Section I.M. above.