Date of Approval: October 1, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-490

Carprofen

Chewable Tablet

Dogs

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:

Dragon Fire Holding Co. Inc.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-490

B. Sponsor

Dragon Fire Holding Co., Inc.,
2619 Skyway Drive
Grand Prairie, TX 75052

Drug Labeler Code: 076033

C. Proprietary Name

Carprofen

D. Drug Product Established Name

carprofen

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

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

H. How Supplied

Scored chewable tablets are packaged in bottles containing 30, 60, or 180 tablets.

I. Dispensing Status

Rx

J. Dosage Regimen

The recommended dosage for oral administration to dogs is 2 mg/lb (4.4 mg/kg) 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 (2.2 mg/kg) twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure. 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

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug (RLNAD)). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

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 tablet sizes. A study was conducted using the 25 mg tablet in dogs, and a waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 75 mg and 100 mg tablets was requested. The study information is summarized below.

A. Canine Blood Level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of carprofen 25 mg chewable tablets.

1. Study Title: Pivotal Two-Way Oral Bioequivalence Study of Two Carprofen Preparations in Beagles

2. Study Dates: October 15, 2014, to April 16, 2015

3. Protocol:
   A randomized, two-period, two-treatment, two-sequence crossover study to evaluate the relative bioavailability of a generic 25 mg chewable tablet formulation of Carprofen compared to an equivalent dose of the RLNAD Rimadyl® (carprofen) chewable tablet (Zoetis Inc., NADA 141-111) in 24 healthy intact, non- pregnant, female beagle dogs.

4. Testing Facility Locations:

   Analytical test facility:
   Pyxant Labs Inc.
   4720 Forge Road, Suite 108
   Colorado Springs, CO 80907

In-life test facility:
Southwest Bio-Labs, Inc. (SBL)
401 N. 17th St., Suite 11
Las Cruces, NM 88005

5. Objectives:

   The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of generic sponsor's 25 mg generic Carprofen chewable tablets and the RLNAD 25 mg Rimadyl® (carprofen) Chewable Tablets in a randomized, two-period, two-treatment, two-sequence crossover study performed in 24 healthy, non-pregnant, female beagle dogs at fasted condition.

6. Measurement and Observation:

   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. All animals remained healthy during the study. No adverse events were recorded.

7. Statistical Methods:

   The study was conducted as a two-period, two-treatment, two-sequence crossover design with 14-day washout between periods. Twenty four female dogs were enrolled in the study and sequence assignment was done completely at random. Primary variables evaluated were area under the curve from time 0 to the first observed concentration below the limit of quantitation (AUC) and maximum concentration (C_{MAX}). Time to maximum concentration (T_{MAX}) is also evaluated.

   Prior to analysis AUC and C_{MAX} were transformed using the natural logarithmic transformation. Ninety percent confidence intervals about the difference of the means for the logarithmically transformed variables (test − reference) were estimated. The endpoints for the confidence interval were back-transformed to geometric means. For the two products to be considered bioequivalent, the back-transformed confidence bounds for both AUC and C_{MAX} must fall between 0.80 and 1.25. As seen in Table 1 below, the bioequivalence criterion is met for both AUC and C_{MAX} and we can conclude that bioequivalence has been established between Dragon Fire Holding Co. Inc. chewable tablet formulation of carprofen (test) and Zoetis Inc.'s Rimadyl® chewable tablet (reference). T_{MAX} values obtained for the test article and RLNAD indicate that these drugs will provide equivalent therapeutic results.

Table 1. Bioequivalence Evaluation

Parameter	Test	Reference	Ratio*	Ratio Lower Bound	Ratio Upper Bound
AUC (ng/mL)*h	275580†	278014†	0.99	.94	1.05
C_{MAX} (ng/mL)	38466†	40547†	0.95	.87	1.03
T_{MAX} (h)	1.417‡	1.313‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean
* Ratio = Test/Reference
NE = not estimated

Bioequivalence between the 25 mg generic Carprofen chewable tablet (test) and the 25 mg RLNAD Rimadyl® (carprofen) chewable tablet (reference) has been established in the *in vivo* bioequivalence study.

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 tablets was requested. To qualify for a biowaiver for each of these product strengths, comparative dissolution studies were conducted to determine the dissolution profiles of Dragon Fire Holding Co. Inc's generic 25 mg, 75 mg, and 100 mg carprofen tablets. The similarity factor (f2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 25 mg (Bio-batch lot p-1264) and generic 25 mg tablets (Pilot batch lot 4850)
- Generic 75 mg and generic 25 mg tablets (both Pilot batch lot 4850)
- Generic 100 mg and generic 25 mg tablets (both Pilot batch lot 4850)

Dissolution parameters:
There is an USP monograph for carprofen tablets dissolution. The paddle speed used in the USP method is 50 rpm. The sponsor developed a dissolution method using a different paddle speed. Twelve vessels filled with dissolution media were placed into the apparatus. Dissolution parameters are as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: phosphate buffer, pH 7.5 $\pm$ 0.05
- Dissolution medium volume: 900 mL
- Temperature: 37.0 ± 0.5°C
- Paddle speed: 100 rpm
- Data Points:
  - 25 mg profile – 5, 15, 20, 30, and 45 minutes
  - 75 and 100 mg profile – 15, 20, 30, 45, and 60 minutes
- Analytical method: HPLC with UV detection

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 both products. The similarity factor (f2) should be greater than 50 to ensure sameness or equivalence of two profiles.

CVM estimated f2 metrics based on mean data, and a summary of the results is presented in the following table:

	Generic 25 mg tablet Bio-batch (lot p-1264)	Generic 75 mg tablet Pilot batch (lot 4850)	Generic 100 mg tablet Pilot batch (lot 4850)
Generic 25 mg tablet Pilot batch (lot 4850)	$f_2 = 54.5$	$f_2 = 70.4$	$f_2 = 54.8$

The comparative dissolution data shows that the 25 mg Pilot batch (lot 4850) is similar ($f_2 > 50$) to the 25 mg Bio-batch (lot p-1264) used in the beagle dog study. Among the different strengths of the Pilot batch (lot 4850), the 75 mg, and 100 mg are similar to the 25 mg tablets Pilot batch (lot 4850).

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. EFFECTIVENESS

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in dogs, which are not food producing animals.

VI. USER SAFETY

CVM did not require user safety studies for this approval.

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

Warnings: Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans.

VII. AGENCY CONCLUSIONS

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that Carprofen, when used according to the label, is safe and effective.