Date of Approval: April 28, 2017

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-595

Carprieve® Chewable Tablets

carprofen

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

Sponsored by:

Norbrook Laboratories, Ltd.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-595

B. Sponsor

Norbrook Laboratories, Ltd.
Station Works, Newry BT35 6JP, Northern Ireland

Drug Labeler Code: 055529

US Agent Name and Address:
Bill Zollers, PhD
Norbrook, Inc.
9401 Indian Creek Parkway, Suite 680
Overland Park, KS 66210

C. Proprietary Name

Carprieve® Chewable Tablets

D. Product Established Name

carprofen

E. Pharmacological Category

Non-steroidal anti-inflammatory

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

25, 75, and 100 mg tablet strengths

H. How Supplied

Each tablet strength is 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 bodyweight 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. Indications

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, an *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD carprofen 75 mg chewable tablets. The RLNAD is available as 25 mg, 75 mg, and 100 mg tablets. An *in vitro* dissolution study was conducted to meet the criteria for a waiver of the requirements to demonstrate bioequivalence for the 25 mg and 100 mg strengths of carprofen chewable tablets. The study information is summarized below.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of carprofen 75 mg oral chewable tablets.

1. Protocol:
   A randomized, two period, two treatment crossover study to evaluate the relative bioavailability of a generic 75 mg chewable tablet formulation of Carprieve® (carprofen) compared to an equivalent dose of the RLNAD RIMADYL® (carprofen) Chewable Tablets (Zoetis Inc., NADA 141-111) in 24 healthy male and female intact beagle dogs.

2. Test Facility Locations:
   Analytical test facility:
   Norbrook Laboratories Limited, Northern Ireland

   In-life test facility:
   Ballyedmond Castle Farms Limited, Northern Ireland

3. Objective:
   The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of Norbrook Laboratories Limited's 75 mg generic Carprieve® (carprofen) Chewable Tablet and the RLNAD 75 mg RIMADYL® (carprofen) Chewable Tablets in a randomized, two period two treatment crossover study in dogs.

4. 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.

5. Statistical Methods:
   The study was conducted as a two-treatment, two-period crossover design with a 33 day washout time between periods. Twenty-four dogs, male and female, were enrolled in the study and sequence assignment was done without respect to sex. Primary variables evaluated are 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 Carprieve® Chewable Tablets (test) and RIMADYL® Chewable Tablets (reference). T_{MAX} values obtained for the test article and RLNAD indicate that these drugs will provide equivalent therapeutic results.

   Table A1: Bioequivalence Evaluation

Parameter	Test	Reference	Ratio*	Ratio Lower Bound	Ratio Upper Bound
AUC (ppm*h)	222.08†	229.89†	0.97	0.89	1.05
C_{MAX} (ppm)	24.14†	22.42†	1.08	0.97	1.20
T_{MAX} (h)	2.38‡	2.05‡	NE	NE	NE

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

Bioequivalence between the 75 mg generic Carprieve® Chewable Tablets (test) and the RLNAD RIMADYL® Chewable Tablets (reference) has been established in the *in vivo* bioequivalence study.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 75 mg carprofen chewable tablet strength.

A waiver of the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 25 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 Norbrook Laboratories, Ltd.'s generic 25 mg, 75 mg, and 100 mg carprofen tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

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

Dissolution parameters:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: Phosphate buffer, pH 7.5
- Dissolution medium volume: 900 mL
- Temperature: 37 °C
- Paddle speed: 100 rpm
- Number of vessels: 12
- Data points: 5, 15, 30, 45, 60, 90, and 120 minutes

The biolots used in the *in vivo* bioequivalence study were the same lots 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 both 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 the following table:

Table B1: Bioequivalence Evaluation

N/A	Generic 25 mg tablet	Generic 100 mg tablet
Generic 75 mg tablet	f_2 = 76	f_2 = 62

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a waiver of the requirement to demonstrate bioequivalence for the generic 25 mg and 100 mg generic carprofen chewable tablets was granted.

In conclusion, bioequivalence was established between generic 75 mg Carprieve® Chewable Tablets (test) and RLNAD RIMADYL® Chewable Tablets (reference) in an *in vivo* bioequivalence study, and the 25 and 100 mg Carprieve® Chewable Tablets were granted a biowaiver based on comparative *in vitro* dissolution studies.

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 Carprieve®:

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 Carprieve®, when used according to the label, is safe and effective.