Date of Approval: June 13, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-555

LIBREVIA

(carprofen)

Soft Chewable Tablets

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:

Piedmont Animal Health

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-555

B. Sponsor

Piedmont Animal Health
204 Muirs Chapel Road, suite 200
Greensboro, NC 27410

Drug Labeler Code: 058147

C. Proprietary Name

LIBREVIA

D. Established Name

carprofen

E. Pharmacological Category

Non-steroidal anti-inflammatory drug

F. Dosage Form:

Soft chewable tablet

G. Amount of Active Ingredient

25, 75, and 100 mg

H. How Supplied

Bottles containing 25 mg x 30 count, 75 mg x 30 count, or 100 mg x 30 count

I. Dispensing Status

Rx

J. Dosage Regimen

2 mg per pound (lb) of body weight once daily or 1 mg/lb twice daily for the control of postoperative pain; administer approximately 2 hours before procedure.

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 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 or 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. Information to show that the generic version is bioequivalent to the approved RLNAD is required for approval.

For this ANADA, an *in vivo* blood-level bioequivalence study was conducted using the test 25 mg carprofen soft chewable tablets and RLNAD carprofen 25 mg tablets to demonstrate product bioequivalence. The RLNAD is available as 25 mg, 75 mg, and 100 mg compressed tablets. The generic product is a soft chewable tablet in 25 mg, 75 mg, and 100 mg strengths. A suitability petition (FDA-2009-P-0462-0001/CP) was granted for the change in dosage form. Additionally, an *in vitro* dissolution study comparison of the test and RLNAD products was conducted to meet the criteria for a waiver of the requirements to demonstrate bioequivalence for the generic 75 mg and 100 mg carprofen soft chewable tablets.

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 (25 mg) tablets.

1. Protocol:

   A randomized, two period, two treatment crossover study to evaluate the relative bioavailability of a test tablet formulation of carprofen (25 mg) compared to an equivalent dose of a commercially available RLNAD RIMADYL (carprofen) tablets (25 mg) in 24 healthy female, non-pregnant beagle dogs.

2. Testing Facility:

   Southwest Bio-Labs, Inc.
   Las Cruces, NM 88005

3. Study Number:

   Piedmont: #009-0051
   Southwest Bio Labs, Inc: #009-01101

4. Objective:

   The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of Piedmont Animal Health, LLC's 25 mg generic carprofen soft chewable tablets and the RLNAD 25 mg RIMADYL (carprofen) tablets in a randomized, two period two treatment crossover study in dogs.

5. Study Summary:

   The study was conducted as a randomized, 2-period, 2-treatment crossover design with a 14 day washout between periods using 24 intact non-pregnant female beagle dogs. Variables evaluated are area under the concentration curve (AUC) from time 0 to the first value below the limit of quantitation, the observed maximum concentration (C_{MAX}), and time to maximum concentration (T_{MAX}). The statistical model included sequence, treatment, and period as fixed effects and animal-within-sequence as a random effect.

   The method for determining bioequivalence is to construct 90% two-sided confidence intervals about the difference of the two means, generic minus RLNAD, based on the natural log scale of AUC and C_{MAX}, and then take the anti-log of the confidence limits. For two products to be bioequivalent, the back transformed confidence bounds for both AUC and C_{MAX} should fall within 0.80-1.25, or be expressed as percentages (80.00%, 125.00%). As seen in Table 1 below, bioequivalence criterion is met for both AUC and C_{MAX}. T_{MAX} values obtained for the test and reference products indicate that these drugs should provide equivalent therapeutic results.

   Table 1. Bioequivalence Evaluation

Variable	Generic Mean	RLNAD Mean	Lower Bound	Upper Bound
AUC (µg/mL)*hour	33970.5*	35152.9*	96.74%	105.49%
C_{MAX} (µg/mL)	1129.0*	1166.1*	88.83%	99.45%
T_{MAX} (hour)	1.25†	1.23†	NA	NA

*Geometric Mean
†Arithmetic Mean

B. Bioequivalence Waiver

A pivotal *in vivo* blood-level bioequivalence study was conducted using the 25 mg carprofen soft chewable tablet strength.

A waiver of the requirement to demonstrate bioequivalence (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 the RLNAD 25 mg tablets as well as the generic 25 mg, 75 mg, and 100 mg tablets. The similarity factor (f2) calculation was used to evaluate dissolution profile comparisons. The dissolution studies compared the following tablets:

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

- Generic 25 mg and generic 100 mg tablets

Dissolution parameters:

Apparatus:	USP/EP apparatus II
Medium:	Phosphate buffer at pH 7.5
Volume:	900 mL vacuum degassed medium
RPM:	100
Temperature:	37°C ± 0.5°C
Data points:	12
Analysis:	HPLC analysis with fluorescence detection

The selection of the apparatus type, *in vitro* testing conditions, and sampling times was based on developing a discriminatory method that could detect significant differences between the dissolution profile of the test and RLNAD products. The biolots used in the *in vivo* bioequivalence study were the same lots of RLNAD and generic products 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.

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

Table 2. Comparison of Dissolution Profiles

	RLNAD 25 mg tablet	Generic 75 mg tablet	Generic 100 mg tablet
Generic 25 mg tablet	f2 = 54	f2 = 57	f2 = 57

In comparing dissolution profiles f2 values ≥50 indicate sameness. The study design requires that no more than 2 data points beyond >85% dissolution be included in the calculation of the f2 metric. Additionally, the percent coefficient of variation for all generic product profiles should fall within the acceptable limits of less than 10%. In cases where both the tablets are >85% dissolved in less than 15 minutes, a dissolution profile comparison using the f2 test is unnecessary. When comparative profiles between tablets do not require an f2 test because of rapid dissolution or when the f2 value is ≥50, the product strength used in the comparison qualifies for a biowaiver.

Study results demonstrate similar dissolution profiles for all comparisons. The percent coefficient of variation for all generic product profiles was less than 10% (data not shown). Therefore, a waiver of the requirement to demonstrate bioequivalence for the generic 75 mg and 100 mg carprofen soft chewable tablets was 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:

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

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