Date of Approval: December 17, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-575

Carprofen 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 in dogs

Sponsored by:

Putney, Inc.

Table of Contents

I. GENERAL INFORMATION:

A. File Number

ANADA 200-575

B. Sponsor

Putney, Inc.
One Monument Sq.
Suite 400
Portland, ME 04101

Drug Labeler Code: 026637

C. Proprietary Name

Carprofen Chewable Tablets

D. Established Name

Carprofen

E. Pharmacological Category

Non-steroidal anti-inflammatory

F. Dosage Form

Scored chewable tablet

G. Amount of Active Ingredient

25 mg, 75 mg, and 100 mg tablets

H. How Supplied

Each tablet strength is packaged in bottles containing 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 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 Chewable Tablets are 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 Chewable Tablets; 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 study was conducted using the test product, Putney, Inc.'s Carprofen Chewable Tablets 25 mg and the reference drug product, RIMADYL Chewable Tablets 25 mg, to demonstrate product bioequivalence. 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 75 mg and 100 mg strengths of Carprofen Chewable Tablets.

A. Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and reference 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 reference drug product, RIMADYL (carprofen) Chewable Tablets (25 mg), sponsored by Zoetis Inc. under NADA 141-111, in 36 healthy, female, non-pregnant beagle dogs.

2. Testing Facility:

Charles River Laboratories Preclinical Services Ireland Ltd.; Glenamoy, Co. Mayo, Ireland.

3. Study Number:

USA014\13-009

4. Objective:

The study was designed to assess the bioequivalence of the test item (Putney Inc.'s Carprofen Chewable Tablets, 25 mg) and a Reference item (RIMADYL (carprofen) Chewable Tablets, 25 mg, Zoetis Inc.) in dogs using a two sequence, two period crossover study design.

5. Study Summary:

The study was conducted as a randomized, two period, two treatment crossover design with a 7 day washout between periods using 36 intact, non-pregnant female, beagle dogs. For the purposes of study management, it was necessary to conduct this study in two sets with 18 animals assigned to each set. Each set was dosed on a different day (one day apart). The pivotal bioequivalence parameters evaluated are area under the concentration curve (AUC) from time 0 to the first value below the limit of quantitation, and the observed maximum concentration (C_{MAX}). The statistical model included treatment, group, and period as fixed effects. The animal nested within group was included as a random effect. The time to maximum concentration (T_{MAX}) is an additional parameter of interest that is assessed by clinical judgment.

The method for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the natural log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. For two products to be bioequivalent the lower confidence bound should be greater than 80.00% and the upper confidence bound should be less than 125.00% for both AUC and C_{MAX}. 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 (ng/mL)*hour	129120.3*	129249.5*	94.7%	105.8%
C_{MAX} (ng/mL)	17014.14*	16802.79*	89.0%	109.5%
T_{MAX} (hour)	2.02†	2.15†	NA	NA

*Geometric Mean
†Arithmetic Mean

B. Bioequivalence Waiver

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

A waiver of the requirement to demonstrate *in vivo* 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 Putney, Inc.'s generic 25 mg, 75 mg, and 100 mg carprofen tablets. The similarity factor (f_2) calculation was used

to evaluate dissolution profile comparisons. The dissolution studies compared the following tablets:

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

Dissolution parameters:

Dissolution apparatus: Apparatus II (paddle)
Dissolution medium: 0.05 M phosphate buffer, pH 7.5
Dissolution medium volume: 900 mL
Temperature in vessel: 37 ± 0.5°C
Paddle speed: 75 rpm
Number of vessels: 12
Sampling time: 5, 10, 20, 30, 45 minutes
Sampling volume: 5 mL
Analytical instrument: HPLC-UV
Detection wavelength: 300 nm

The biolot 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 (%CV) at the earlier time point (e.g., 5 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 less than 10% (data not shown). 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:

	Generic 75 mg tablet	Generic 100 mg tablet
Generic 25 mg tablet	$f_2 = 73$	$f_2 = 62$

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a waiver of the requirement to demonstrate bioequivalence for the generic 75 mg and 100 mg carprofen 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 Carprofen Chewable Tablets:

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