Date of Approval: September 5, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-795

CARPROFEN Soft Chewable Tablets

(carprofen)

Dogs

CARPROFEN Soft 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.

Sponsored by:

Felix Pharmaceuticals Pvt. Ltd.

Executive Summary

CARPROFEN Soft 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

For this approval, the Food and Drug Administration (FDA) approved a suitability petition to allow the sponsor to submit an abbreviated new animal drug application (ANADA) for a generic animal drug that differs in the dosage form from the RLNAD. The dosage form of the RLNAD is a compressed tablet. The dosage form of the generic product is a soft chewable tablet.

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 25 mg CARPROFEN Soft Chewable Tablets are bioequivalent to the 25 mg RIMADYL® chewable tablets. 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 soft 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 Soft Chewable Tablets, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-795

B. Sponsor

Felix Pharmaceuticals Pvt. Ltd.
25-28 North Wall Quay
Dublin 1, Ireland

Drug Labeler Code: 086101

U.S. Agent Name and Address:

Sharon G. Chase, DVM, MPH
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

CARPROFEN Soft Chewable Tablets

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, or 100 mg of carprofen per tablet

H. How Supplied

Each tablet size is scored and contains 25 mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 30 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 Soft Chewable Tablets are scored and dosage should be calculated in half-tablet increments.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

CARPROFEN Soft 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®; 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 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.

The sponsor submitted a suitability petition (FDA-2016-P-1991) requesting permission to submit an ANADA for a generic new animal drug that differed in dosage form from the RLNAD. The dosage form of the generic product is a soft chewable tablet. The dosage form of the RLNAD is a compressed chewable tablet. This petition was approved on September 21, 2016, under 512(n)(3)(C) of the FD&C Act.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic soft chewable and RLNAD (carprofen) chewable 25 mg tablet. The RLNAD is available in 25, 75, and 100 mg tablet sizes. The *in vivo* blood-level study was conducted in 28 healthy, fasted beagle 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 tablet and the 25 mg generic carprofen soft chewable tablet by the average bioequivalence approach as described in the Statistical Method section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 75 mg and 100 mg soft chewable tablets was requested. Dissolution data was used to demonstrate that the generic 75 mg and 100 mg

soft chewable tablet are comparable to the RLNAD 75 mg and 100 mg chewable tablets, respectively. Therefore, a biowaiver for the generic 75 mg and 100 mg generic carprofen soft chewable tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of RIMADYL® Chewable Tablets and a Generic Formulation of Carprofen Soft Chewable Tablets when Administered Orally to Beagle Dogs. (Study No. 080-BC-1918)

Study Dates: June 18, 2021 to January 12, 2022

Study Locations:

In-life phase: Ontario, Canada

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 Soft Chewable Tablets and the RLNAD 25 mg RIMADYL® (carprofen) chewable tablets in fasted Beagle dogs.

Study Animals: Twenty-eight intact male Beagle dogs, greater than 6 months old (503 to 1260 days), and weighing 10.1 to 13.0 kg.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 25 mg of either the generic or RLNAD carprofen chewable tablet 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 28 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. 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 (ng/mL)*min	10640.9†	11293.0	0.94	0.89	0.99
C_{MAX} (ng/mL)	21.5†	21.3†	1.01	0.94	1.08
T_{MAX} (min) (SD)‡	58.9 (36.5)‡	58.9 (29.4)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
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 Soft 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 soft chewable tablet 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 and RLNAD 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 RLNAD 25 mg tablets
- Generic 75 mg and RLNAD 75 mg tablets
- Generic 100 mg and RLNAD 100 mg tablets

The objective was to satisfy f_2 criteria between the generic tablet strengths to the corresponding RLNAD tablet strengths. The analytical method and dissolution conditions were determined to be adequately validated.

The dissolution conditions were as follows:

- Dissolution apparatus: USP Method 2 (peak vessels)
- Dissolution medium: Phosphate buffer, pH 7.5
- Dissolution medium volume: 900 mL
- Temperature: 37 °C + 0.5°C
- Paddle speed: 50 rpm
- Number of vessels: 12
- Data points: 10, 15, 30, 45, 60, and 90 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 and the RLNAD 25 mg chewable tablet 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.

The Center for Veterinary Medicine (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 25 mg RLNAD	73.72
75 mg generic to the 75 mg RLNAD	70.45
100 mg generic to the 100 mg RLNAD	60.62

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 75 mg and 100 mg carprofen soft chewable tablet 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 Soft Chewable Tablets:

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 Soft Chewable Tablets, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.