Date of Approval: January 5, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-732

Carprofen Tablets

Caplets

Dogs

Carprofen 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 Tablets are approved to relieve pain and inflammation associated with osteoarthritis in dogs; and to control postoperative pain associated with both soft tissue and orthopedic surgeries in dogs. Carprofen Tablets are a generic version of RIMADYL®.

	Proprietary Name	**Established Name**	**Application Type and Number**	**Sponsor**
Generic Animal Drug	Carprofen Tablets	carprofen tablets	Abbreviated New Animal Drug Application (ANADA) 200-732	Felix Pharmaceuticals Pvt. Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	RIMADYL®	carprofen tablets	New Animal Drug Application (NADA) 141-053	Zoetis Inc.

Carprofen is in the propionic acid class of non-narcotic, non-steroidal anti-inflammatory drugs (NSAIDs) and has characteristic analgesic and antipyretic activity. Like many NSAIDs, carprofen works by inhibiting the enzyme cyclooxygenase, which in turn, leads to decreased synthesis of prostaglandins. Prostaglandins contribute to pain, fever, and inflammation throughout the body, among other functions.

Bioequivalence
The Federal Food, Drug, and Cosmetic (FD&C) Act allows an animal drug sponsor to submit an abbreviated new animal drug application (ANADA) for a generic version of an approved brand name animal drug (also called the reference listed new animal drug or RLNAD). This law typically requires the sponsor to show that the generic drug is bioequivalent to the approved RLNAD. Broadly, bioequivalence means the generic drug is absorbed by and performs the same way in the animal's body as the RLNAD, which has already been shown to be safe and effective when used according to the label. The FD&C Act doesn't require the sponsor to submit new effectiveness or target animal safety data in the ANADA for a generic animal drug.

The sponsor conducted one *in vivo* blood-level study in fasted dogs to show that the 25 mg Carprofen Tablets are bioequivalent to the 25 mg RIMADYL® tablets. No serious adverse events were reported during the study.

The sponsor also conducted comparative *in vitro* dissolution studies comparing the dissolution profiles for the 75 mg and 100 mg Carprofen Tablets to the dissolution profile for the 25 mg Carprofen Tablets. The 25 mg Carprofen Tablets were used as the comparator because they were shown to be bioequivalent to the 25 mg RIMADYL® tablets in the *in vivo* blood-level study. Because all strengths had similar dissolution profiles, the 75 mg and 100 mg tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). Therefore, FDA granted a biowaiver for these strengths.

Conclusions
Based on the data submitted by the sponsor for the approval of Carprofen 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 200-732

B. Sponsor

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

Drug Labeler Code: 086101

U.S. Agent Name and Address:
James H. Schafer, DVM
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

Carprofen Tablets

D. Drug Product Established Name

carprofen tablets

E. Pharmacological Category

Non-steroidal anti-inflammatory drug

F. Dosage Form

caplet

G. Amount of Active Ingredient

25 mg, 75 mg, or 100 mg of carprofen per caplet

H. How Supplied

Each caplet strength is scored and packaged in bottles containing 30, 60, or 180 caplets.

I. Dispensing Status

Prescription (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.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Carprofen 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 tablets; NADA 141-053; Zoetis Inc.

II. BIOEQUIVALENCE

The 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.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD 25 mg carprofen tablets. The RLNAD is available in 25, 75, and 100 mg tablet sizes. The *in vivo* blood-level study was conducted in 24 healthy, fasted 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 RLNAD carprofen tablets and the 25 mg generic carprofen tablets by the average bioequivalence approach as described in the Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 75 mg and 100 mg tablets was requested. Dissolution data was used to demonstrate that the generic 75 mg and 100 mg carprofen tablets are comparable to the generic 25 mg tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 75 mg and 100 mg carprofen tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of RIMADYL® Caplets and a Generic Formulation of Carprofen Caplets when Administered Orally to Beagle Dogs. (Study No. 080-BC-2219)

Study Dates: May 28, 2020 to October 30, 2020

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

Study Animals: 24 intact male beagle dogs, approximately 420 to 1247 days of age on study Day 0 and weighing between 8.2 to 11.7 kg on study day -4.

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 tablets 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 Methods:

The laboratory study was conducted as a randomized, masked, two-period, two sequence, two-treatment, single-dose crossover design using 24 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 (µg/mL)*hour	201†	212†	0.95	0.91	0.99
C_{MAX} (µg/mL)	24.46†	25.10†	0.97	0.94	1.01
T_{MAX} (hours) (SD)‡	0.96 (0.39)‡	0.88 (0.49)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic/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 Tablets and the RLNAD 25 mg RIMADYL® (carprofen tablets) are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood-level bioequivalence study was conducted using the 25 mg carprofen tablets 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 *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic 25 mg, 75 mg, and 100 mg carprofen tablets. Comparisons were made between the following tablets:

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

The objective was to satisfy similarity factor (f_2) criteria between the generic 25 mg tablet strength and the generic 75 mg and 100 mg tablet strengths.

Test conditions were as follows:
- Dissolution apparatus: USP Apparatus II
- Dissolution medium: Phosphate buffer, pH 7.5
- Dissolution medium volume: 900 mL
- Temperature: 37 ± 0.5°C
- Paddle speed: 50 rpm
- Number of vessels: 12

- Data points: 5, 10, 15, 20, 30, and 45 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. 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 f_2 should be greater than 50 to ensure sameness or equivalence of two profiles.

Study results demonstrate similar dissolution profiles for all comparisons. However, because of rapid dissolving characteristics (>85% in 15 minutes) in all strengths, a dissolution profile comparison using the f_2 test is unnecessary. When comparative profiles between tablets do not require an f_2 test because of rapid dissolution or when the f_2 value is ≥50, the product strengths used in the comparison qualify for a biowaiver. Therefore, a biowaiver for the generic 75 mg and 100 mg carprofen tablets 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 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 Tablets, when used according to the label, are safe and effective for the indications listed in Section I.M. above.