

Date of Approval: January 12, 2024

FREEDOM OF INFORMATION SUMMARY
ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-767

Carprofen Tablets

Flavored Tablets

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 flavored 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 tablets) caplets, sponsored by Zoetis Inc., under NADA 141-053.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 25 mg carprofen flavored tablet is bioequivalent to the 25 mg RIMADYL® caplets. 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 and 100 mg flavored 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 Tablets, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-767

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

Flavored tablet

G. Amount of Active Ingredient

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

H. How Supplied

Carprofen Tablets are scored, and contain 25 mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 30, 60, or 180 tablets.

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. Tablets are scored and dosage should be calculated in half-tablet increments.

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 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 abbreviated new animal drug application (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 certain dosage forms, the agency will grant a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD (carprofen) 25 mg flavored tablet. The RLNAD is available in 25, 75, and 100 mg dosage form sizes. The *in vivo* blood-level study was conducted in 26 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) caplets and the 25 mg generic (carprofen tablets) flavored 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 dosage form was requested.

Dissolution data was used to demonstrate that the RLNAD 75 mg and 100 mg carprofen tablets are comparable to the generic 25 mg tablet used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 75 mg and 100 mg generic carprofen tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of Rimadyl® Tablets and a Generic Formulation of Carprofen Flavoured Tablets when Administered Orally to Beagle Dogs in a Fasted State. (Study No. CARF-KC2-6822)

Study Dates: December 21, 2022 to May 18, 2023

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) caplets in fasted dogs.

Study Animals: 26 purpose-bred, intact male, beagle dogs, ages 11 months to 3 years and weighing 9.8 kg to 12.1 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 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 26 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	194.0 [†]	202.5 [†]	0.96	0.92	1.00
C_{MAX} (µg /mL)	21.5 [†]	24.1 [†]	0.89	0.84	0.95
T_{MAX} (hours) (SD) [‡]	1.00 (0.56) [‡]	0.90 (0.46) [‡]	NE	NE	NE

[†] Geometric mean

[‡] Arithmetic mean and standard deviation (SD)

[◇] Ratio = Generic/RLNAD

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) caplets are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg carprofen tablet 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 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 the 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°C ± 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 batch 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, is safe and effective for the conditions of use in the General Information Section above.