Date of Approval: August 3, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-755

Firocoxib

Chewable Tablet

Dogs

Firocoxib chewable tablets are indicated for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs.

Sponsored by:

Felix Pharmaceuticals Pvt. Ltd.

Executive Summary

Firocoxib chewable tablets are approved for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs. The reference listed new animal drug (RLNAD) is Previcox® chewable tablets sponsored by Boehringer Ingelheim Animal Health USA, Inc. under NADA 141-230.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 57 mg Firocoxib is bioequivalent to the 57 mg Previcox®. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strength. Based on the dissolution data, the 227 mg chewable tablet qualified for a waiver from the requirement to perform a separate *in vivo* bioequivalence study (a biowaiver). FDA granted a biowaiver for this strength.

Conclusions

Based on the data submitted by the sponsor for the approval of Firocoxib, 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 200-755

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

Firocoxib

D. Drug Product Established Name

firocoxib

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

57 mg or 227 mg of firocoxib per tablet

H. How Supplied

Each tablet strength is half-scored and supplied in 60 count and 180 count bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The recommended dosage of Firocoxib for oral administration in dogs is 2.27 mg/lb (5.0 mg/kg) body weight once daily as needed for osteoarthritis and for 3 days as needed for postoperative pain and inflammation associated with soft-tissue and

orthopedic surgery. The dogs can be treated with Firocoxib approximately two hours prior to surgery. The tablets are scored and dosage should be calculated in half tablet increments. Firocoxib chewable tablets can be administered with or without food. Use the lowest effective dose for the shortest duration consistent with individual response.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Firocoxib chewable tablets are indicated for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs.

N. Reference Listed New Animal Drug

Previcox®; firocoxib; NADA 141-230; Boehringer Ingelheim Animal Health USA, 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 this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD firocoxib 57 mg chewable tablets. The RLNAD is available in 57 and 227 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 32 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 RLNAD 57 mg firocoxib chewable tablets and the generic 57 mg firocoxib chewable tablets by the mixed reference-scaled average bioequivalence approach as described in the Statistical Methods section below. A biowaiver for the generic 227 mg chewable tablet was requested. Dissolution data was used to demonstrate that the generic 227 mg firocoxib chewable tablets are comparable to the generic 57 mg chewable tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 227 mg firocoxib chewable tablet was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of Previcox® Chewable Tablets and a Formulation of Generic Firocoxib Tablets when Administered Orally to Dogs. (Study No. FIRH-KC2-4421)

Study Dates: July 30, 2021 to March 22, 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 57 mg Firocoxib and the RLNAD 57 mg Previcox® (firocoxib) in fasted dogs.

Study Animals: 32 intact male beagles, weighing approximately 10 – 12 kg, and approximately 1.5 years to 3 years of age.

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

Drug Administration: Each animal received 57 mg of either the generic or RLNAD firocoxib according to their randomized treatment sequence (generic/RLNAD/generic/RLNAD or RLNAD/generic/RLNAD/generic).

Measurements and Observations: The plasma concentrations of firocoxib 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 four-period, two-sequence, two-treatment, single-dose crossover design using 32 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.

The mixed reference-scaled average bioequivalence approach (RSABE) was used to evaluate bioequivalence. Prior to the analysis, C_{MAX} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (s_{WR}) of the RLNAD was calculated separately for transformed C_{MAX} and AUC to select the appropriate analysis approach based on FDA Guidances.

- The s_{WR} was less than 0.294 for AUC, so the average bioequivalence method was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and a random effect of subject nested within

sequence. Period was modeled as a repeated factor. Bioequivalence was established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratios (generic:RLNAD) were contained within the acceptance limits of 0.80 to 1.25.

- The s_{WR} was equal to or greater than 0.294 for C_{MAX}, so the RSABE method was used, and bioequivalence was established based on the following two criteria:

  - The estimated 95% upper confidence bound for $(\mu_T-\mu_R)^2- \theta^*\sigma^2_{WR}$ is less than zero (0), where μ_T and μ_R are the population means of the natural log transformed primary variable for the generic article and RLNAD, respectively, $\theta = (\log (1.25)/\sigma_{W0})^2$ and $\sigma_{W0} = 0.25$.

  - The point estimate of the generic to RLNAD geometric mean ratio is contained within the acceptance limits of 0.80 and 1.25.

Results:

As seen in the tables below, 90% confidence interval for AUC falls within the prescribed bound (Table II.1), and C_{MAX} ratio falls within the prescribed bound, and the 95% upper bound of the expression is less than zero (Table II.2). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation – AUC

Parameter	Generic Mean	RLNAD Mean	Ratio[◊]	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	10510[†]	9781[†]	1.075	0.973	1.187

[†] Geometric mean
[◊] Ratio = Test/Reference
CI = confidence interval

Table II.2. Bioequivalence Evaluation – C_{MAX} and T_{MAX}

Parameter	S_{WR}	Generic Mean	RLNAD Mean	Ratio[◊]	Upper 95% bound[$]
C_{MAX} (ng/mL)	0.3330	797[†]	736[†]	1.083	-0.0422
T_{MAX} (hours) (SD)[‡]	NE	3.49 (4.75)[‡]	4.29 (5.35)[‡]	NE	NE

[†] Geometric mean
[‡] Arithmetic mean and standard deviation (SD)
[◊] Ratio = Test/Reference
[$]Confidence interval for $(\mu_T-\mu_R)^2- \theta^*\sigma^2_{WR}$
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 57 mg Firocoxib chewable tablets and the RLNAD 57 mg Previcox® (firocoxib) chewable tablets are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 57 mg firocoxib chewable tablet strength. A biowaiver for the 227 mg chewable tablet was requested. To qualify for a biowaiver for this product strength, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic 57 mg and 227 mg and RLNAD 57 mg firocoxib chewable tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 57 mg and generic 227 mg tablets
- Generic 57 mg and RLNAD 57 mg tablets

The objective was to satisfy f_2 criteria between the generic 57 mg tablet strength and the generic 227 mg tablet strength.

Test conditions were as follows:

- Dissolution apparatus: USP Type 2 (Paddle)
- Dissolution medium: 0.1N HCL with 0.5% w/v sodium lauryl sulfate (SLS) in water
- Dissolution medium volume: 1000 mL
- Temperature: 37.0 ± 0.5°C
- Paddle speed: 75 rpm
- Data points: 10, 15, 20, 30, 45, 60, 90, and 120 minutes

The generic drug lot number used in the *in vivo* bioequivalence study was the same lot used in the comparative dissolution study 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.

CVM estimated f_2 metrics based on mean data, and a summary of the results is presented in Table II.3 below:

Table II.3. Similarity Results

Dissolution Comparison	Similarity Results
57 mg generic to the 227 mg generic	69.897
57 mg generic to the 57 mg RLNAD	54.402

Study results demonstrate similar dissolution profiles for both comparisons. Therefore, a biowaiver for the generic 227 mg firocoxib 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 Firocoxib:

Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case 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 Firocoxib, when used according to the label, is safe and effective for the indications listed in Section I.M. above.