Date of Approval: August 3, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-756

Firodyl™

(firocoxib)

Chewable Tablet

Dogs

Firodyl™ (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:

Ceva Sante Animale

Executive Summary

Firodyl™ (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. The reference listed new animal drug (RLNAD) is Previcox® (firocoxib) 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 Firodyl™ 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 separate *in vivo* bioequivalence studies (a biowaiver). FDA granted a biowaiver for this strength.

Conclusion

Based on the data submitted by the sponsor for the approval of Firodyl™, 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 200-756

B. Sponsor

Ceva Sante Animale
10 Avenue de la Ballastière,
33500 Libourne, France

Drug Labeler Code: 013744

C. Proprietary Name

Firodyl™

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 and 227 mg of firocoxib per tablet

H. How Supplied

Half-scored tablets in two strengths, containing 57 mg or 227 mg firocoxib. Each tablet strength is supplied in 60 count and 180 count bottles.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The recommended dosage of Firodyl™ (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 Firodyl™ approximately two hours prior to surgery. The tablets are scored and dosage should be calculated in half tablet increments. Firodyl™ 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

Firodyl™ (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 a 57 and 227 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 24 healthy, fed 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 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 strength was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of PREVICOX® (firocoxib chewable tablets) and a Generic Firocoxib Chewable Tablet in Beagle Dog. (Study No. 03-BQ-C-2004)

Study Dates: January 11, 2021 – August 4, 2021

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Middleton, WI

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 57 mg Firodyl™ (firocoxib) chewable tablets and the RLNAD 57 mg Previcox® (firocoxib) chewable tablets in fed dogs.

Study Animals: 24 intact male beagle dogs, 14-16 months of age, and weighing between 10.2 to 13.6 kg.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies (US CFR Title 21, Part 58).

Drug Administration: Each animal received 57 mg of either the generic or RLNAD firocoxib according to their randomized treatment sequence (generic/RLNAD or 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 two-period, two-sequence, two-treatment, single-dose crossover design using 24 healthy male 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)*hour	18324†	20978†	0.87	0.85	0.90
C_{MAX} (ng/mL)	1863†	2184†	0.85	0.82	0.88
T_{MAX} (hours) (SD)‡	1.44 (0.3)‡	1.51 (0.06)‡	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 57 mg Firodyl™ (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 generic 227 mg chewable 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 57 mg and generic 227 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 chewable tablets

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

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.5% Sodium lauryl sulfate (SLS) in water
- Dissolution medium volume: 1000 mL
- Temperature: 37.0 ± 0.5°C
- Paddle speed: 75 rpm
- Number of vessels: 12

- Data points: 10, 15, 20, 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. 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.2 below:

Table II.2. Similarity Results

Dissolution Comparison	Similarity Results
57 mg generic to the 227 mg chewable tablets	59.3

Study results demonstrate similar dissolution profiles. Therefore, a biowaiver for the generic 227 mg firocoxib chewable 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 Firodyl™:

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 Firodyl™, when used according to the label, is safe and effective for the indications listed in Section I.M. above.