Date of Approval: March 28, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-722

Firox™

(firocoxib)

Chewable Tablets

Dogs

Firox™ (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:

Norbrook Laboratories, Ltd.

Executive Summary

Firox™ (firocoxib) Chewable Tablets are approved to control pain and inflammation associated with osteoarthritis in dogs; and to control postoperative pain associated with both soft tissue and orthopedic surgeries in dogs. Firox™ chewable tablets are a generic version of Previcox® chewable tablets.

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Firox™	firocoxib	Abbreviated New Animal Drug Application (ANADA) 200-722	Norbrook Laboratories, Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	Previcox®	firocoxib	New Animal Drug Application (NADA) 141-230	Boehringer Ingelheim Animal Health USA, Inc.

Firocoxib is in the coxib class of non-narcotic, nonsteroidal anti-inflammatory drugs (NSAIDs). Like many NSAIDs, firocoxib 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 healthy, fasted dogs to show that the 57 mg Firox™ chewable tablets are bioequivalent to the 57 mg Previcox® chewable tablets. No serious adverse events were reported during the study.

Previcox® is available in 57 and 227 mg chewable tablets. The sponsor conducted comparative *in vitro* dissolution studies comparing the dissolution profile of the 227 mg generic tablets to the dissolution profile of the 57 mg generic chewable tablets. The 57 mg generic chewable tablet was used as the comparator because it was shown to be bioequivalent to the 57 mg Previcox® chewable tablet in the *in vivo* blood-level study. The dissolution profiles for both strengths were similar. Therefore, the 227 mg generic chewable tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver), and FDA granted a biowaiver for this strength.

Conclusions
Based on the data submitted by the sponsor for the approval of Firox™, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION 5
II. BIOEQUIVALENCE 6
III. HUMAN FOOD SAFETY 9
IV. USER SAFETY 9
V. AGENCY CONCLUSIONS 10

I. GENERAL INFORMATION

A. File Number

ANADA 200-722

B. Sponsor

Norbrook Laboratories, Ltd.
Carnbane Industrial Estate
Newry, County Down
BT35 6QQ UNITED KINGDOM

Drug Labeler Code: 055529

U.S. Agent Name and Address:
Ms. Melanie Archer
Norbrook, Inc.
9401 Indian Creek Parkway
Suite 680
Overland Park, Kansas 66210

C. Proprietary Name

Firox™

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

Firox™ is available as 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 Firox™ (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 Firox™ approximately two hours prior to surgery. The tablets are scored and dosage should be calculated in half tablet increments. Firox™ 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. Indications

Firox™ (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 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 firocoxib 57 mg chewable tablet strengths. The RLNAD is available in 57 and 227 mg tablet strengths. The *in vivo* blood-level study was conducted in 40 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 57 mg Previcox® (firocoxib) chewable tablet and the 57 mg generic firocoxib chewable tablet by the average bioequivalence approach as described in the Statistical Methods section below. A biowaiver for the generic 227 mg chewable tablet strength was requested. Dissolution data was used to demonstrate that the generic 227 mg firocoxib tablets are comparable to the generic 57 mg tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 227 mg firocoxib tablet strength was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

One *in vivo* blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of firocoxib chewable tablets (57 mg).

Title: A four-period crossover pharmacokinetic study to determine the plasma levels of firocoxib in dogs following oral administration of Firocoxib Chewable Tablets 57 mg (Norbrook Laboratories Limited, Product Code: T-FIR-050) and Previcox® Chewable Tablets 57 mg (Merial Ltd., Inc., NADA 141-230). (Study No. 026/18).

Study Dates: August 28, 2018 to February 19, 2019

Study Locations:

In-life phase: Co. Down, Northern Ireland

Bioanalytical testing: Co. Down, Northern Ireland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence for the generic 57 mg Firox™ (firocoxib) and the RLNAD 57 mg Previcox® (firocoxib) in fasted dogs. The study was conducted according to UK Good Laboratory Practice Standards, as amended by Statutory Instrument 2004/994, which are in accordance with Organization for Economic Cooperation and Development Principles of Good Laboratory Practice.

Study Animals: 40 healthy purpose-bred male and female, intact or spayed/neutered beagles, aged 2 to 12 years.

Experimental Design: A randomized, masked, four-period, two-sequence, two treatment, single-dose crossover study.

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 40 dogs with 21-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 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} is less than 0.294 for both C_{MAX} and AUC, so the average BE 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 is established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratio (generic:RLNAD) contained within the acceptance limits of 0.80 to 1.25.

Table II.1. Bioequivalence Evaluation

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 90% CI	Upper 90% CI
AUC (µg/mL)*hour	10.91†	10.38†	1.050	0.975	1.132
C_{MAX} (µg/mL)	0.79†	0.77†	1.056	0.951	1.172
T_{MAX} (hours) (SD)‡	2.88 (4.35)‡	2.50 (3.59)‡	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 Firox™ (firocoxib) chewable tablet and the RLNAD 57 mg Previcox® (firocoxib) chewable tablet 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 waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 227 mg 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 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

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:

- Apparatus: USP Type 2 (paddles)
- Temperature: 37 ± 0.5°C
- Paddle speed: 50 rpm
- Dissolution medium: acetate buffer + 1% Cetrimide.
- pH: 4.5 ± 0.05
- Dissolution medium volume: 900 mL ± 9 mL
- Filter: 0.22 µm PTFE syringe filter
- Sampling time points: 5, 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 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 both 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 (f_2) Results

Dissolution Comparison	f_2 (≥ 50 indicates sameness)
57 mg generic to the 227 mg generic	57.4

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 227 mg firocoxib chewable tablet strength 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 Firox™:

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. For use in dogs only.

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