

Date of Approval: June 14, 2021

FREEDOM OF INFORMATION SUMMARY
ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-704

Deracoxib Chewable Tablets

(deracoxib)

Dogs

Deracoxib Chewable Tablets are indicated in dogs for the control of pain and inflammation associated with osteoarthritis, for the control of postoperative pain and inflammation associated with orthopedic surgery, and for the control of postoperative pain and inflammation associated with dental surgery.

Sponsored by:

Felix Pharmaceuticals Pvt. Ltd.

Executive Summary

Deracoxib Chewable Tablets (deracoxib) are approved to control pain and inflammation associated with osteoarthritis in dogs; and to control postoperative pain and inflammation associated with orthopedic surgery and dental surgery in dogs. The drug is a generic version of Deramaxx™.

Product	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Deracoxib Chewable Tablets	deracoxib	Abbreviated New Animal Drug Application (ANADA) 200-704	Felix Pharmaceuticals Pvt. Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	Deramaxx™	deracoxib	New Animal Drug Application (NADA) 141-203	Elanco US Inc.

Deracoxib Chewable Tablets are in the coxib class of non-narcotic, nonsteroidal anti-inflammatory drugs (NSAIDs). Like many NSAIDs, deracoxib 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 Deracoxib Chewable Tablets are bioequivalent to the 25 mg Deramaxx™ chewable tablets. No serious adverse events were reported during the study.

Deramaxx™ is available in 12, 25, 50, 75, and 100 mg chewable tablets; however, the 50 mg tablet is not currently marketed. The sponsor conducted one comparative *in vitro* dissolution study comparing the dissolution profiles for the 12, 75, and 100 mg generic chewable tablets to the dissolution profile for the 25 mg generic chewable tablet. The 25 mg generic chewable tablet was used as the comparator because it was shown to be bioequivalent to the 25 mg Deramaxx™ chewable tablet in the *in vivo* blood-level study. All comparisons showed similar dissolution profiles. Therefore, the 12, 75, and 100 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 these strengths.

Conclusions

Based on the data submitted by the sponsor for the approval of Deracoxib Chewable 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 200-704

B. Sponsor

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

Drug Labeler Code: 086101

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

C. Proprietary Name

Deracoxib Chewable Tablets

D. Drug Product Established Name

deracoxib

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

12 mg, 25 mg, 75 mg, or 100 mg of deracoxib per tablet

H. How Supplied

Tablets are available as 12 mg, 25 mg, 75 mg and 100 mg round, brownish, half-scored tablets in 30 and 90 count bottles.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Osteoarthritis Pain and Inflammation: 0.45 - 0.91 mg/lb/day (1 to 2 mg/kg/day) as a single daily dose, as needed.

Postoperative Orthopedic Pain and Inflammation: 1.4 – 1.8 mg/lb/day (3 to 4 mg/kg/day) as a single daily dose, as needed, not to exceed 7 days of administration.

Postoperative Dental Pain and Inflammation: 0.45 – 0.91 mg/lb/day (1 to 2 mg/kg/day) as a single daily dose, for 3 days.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

Deracoxib Chewable Tablets are indicated in dogs for the control of pain and inflammation associated with osteoarthritis, for the control of postoperative pain and inflammation associated with orthopedic surgery, and for the control of postoperative pain and inflammation associated with dental surgery.

N. Reference Listed New Animal Drug

Deramaxx™; deracoxib; NADA 141-203; Elanco US 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 deracoxib 25 mg chewable tablets. The RLNAD is approved in 12, 25, 50, 75, and 100 mg chewable tablet sizes. The 50 mg strength for the RLNAD is not currently marketed. 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 and the 25 mg generic deracoxib chewable tablets by the mixed reference-scaled 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 12 mg, 75 mg, and 100 mg chewable tablets was requested. Dissolution data was used to demonstrate that the generic 12 mg, 75 mg, and 100 mg 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 12 mg, 75 mg, and 100 mg deracoxib chewable tablets was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of deracoxib chewable tablets (25 mg).

Title: Pivotal Bioequivalence Study of Deramaxx® Tablets and a Generic Formulation of Deracoxib when Administered Orally to Dogs. (Study No. 080-BC-3717)

Study Dates: August 9, 2018 to January 25, 2019

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 and RLNAD 25 mg deracoxib chewable tablets in fasted dogs.

Study Animals: 24 intact female dogs, age 8 months to 2.5 years

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

Drug Administration: Each animal received 25 mg of either the generic or RLNAD according to their randomized treatment sequence: generic-RLNAD-generic-RLNAD, or RLNAD-generic-RLNAD-generic.

Measurements and Observations: The plasma concentrations of deracoxib 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 Method:

The laboratory study was conducted as a randomized, masked, four-period, two-sequence, two-treatment, single-dose crossover design using 24 dogs with a 14-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 greater than 0.294 for both C_{MAX} and AUC, so the RSABE method was used and bioequivalence was established based on the following two criteria:
 - The estimated 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta * \sigma_{WR}^2$ 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, σ_{WR} is the population with-in subject standard deviation for RLNAD, $\theta = (\log(1.25)/\sigma_{w0})^2$ 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:

Table II.1. Bioequivalence Evaluation

Parameter	s_{WR}^\dagger	Ratio [‡]	Upper 95% Bound [◊]
AUC (ng*hr/mL)	0.3229	0.99	-0.0529
C_{MAX} (ng/mL)	0.3973	1.03	-0.0767

[†]estimated within-subject standard deviation of the RLNAD

[‡]point estimate of the geometric mean ratio (Generic/RLNAD)

[◊]estimated 95% upper confidence bound of $(\mu_T - \mu_R)^2 - \theta * \sigma_{WR}^2$

The arithmetic mean of T_{MAX} is 2.3 hours for both generic article and RLNAD.

Adverse Reactions: There were no serious adverse events reported during the study.

Conclusion: The *in vivo* bioequivalence study demonstrated that 25 mg chewable tablets of deracoxib are bioequivalent for the generic and RLNAD in dogs.

B. Bioequivalence Waiver

A pivotal *in vivo* blood-level bioequivalence study was conducted using the generic 25 mg deracoxib chewable tablet strength. A biowaiver for the generic 12 mg, 75 mg, and 100 mg deracoxib 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 12 mg, 75 mg, and 100 mg deracoxib tablets. Where appropriate the similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following chewable tablets:

- Generic 12 mg tablets and generic 25 mg tablets
- Generic 75 mg tablets and the RLNAD 75 mg tablets

- Generic 100 mg tablets and the RLNAD 100 mg tablets

The objective was to satisfy f_2 criteria between the generic tablet strengths (12 mg, 75 mg and 100 mg) and the generic tablet strength used in the *in vivo* blood-level bioequivalence study (25 mg), or to the corresponding RLNAD tablet strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Method 2 (paddles)
- Dissolution medium: 0.1N HCl (pH = 1.2) + 0.5% SLS.
- Dissolution media volume: 900 mL
- Temperature: 37 °C + 0.5 °C
- Paddle: speed: 50 rpm
- Number of vessels: 12
- Data points: 10, 15, 20, 30, 45, 60, and 90 minutes.

For the *in vitro* profile comparison of the 12 mg tablet to the 25 mg tablet, 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 (f_2) Results

Dissolution Comparison	Similarity Results
12 mg generic to the 25 mg generic	> 85% dissolved within 15 minutes, supports sameness, f_2 not applicable
75 mg generic to the 75 mg RLNAD	66
100 mg generic to the 100 mg RLNAD	62

Study results demonstrate similar dissolution profiles for all comparisons. However, because of rapid dissolving characteristics (> 85% in 15 minutes) in 12 mg and 25 mg 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 12 mg, 75 mg, and 100 mg deracoxib 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 Deracoxib Chewable Tablets:

Not for use in humans. Keep this and all medications out of 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 Deracoxib Chewable Tablets, when used according to the label, is safe and effective for the indications listed in Section I.M. above.