

Date of Approval: February 4, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-637

Doxidyl™

deracoxib

Chewable Tablets

Dogs

For the control of pain and inflammation associated with osteoarthritis in dogs, for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs and for the control of postoperative pain and inflammation associated with dental surgery in dogs.

Sponsored by:

Provetica AH LLC

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I. GENERAL INFORMATION

A. File Number

ANADA 200-637

B. Sponsor

Provetica AH LLC
455 Sovereign Court
Baldwin, MO 63011

Drug Labeler Code: 086097

C. Proprietary Name

Doxidy|™

D. Drug Product Established Name

deracoxib

E. Pharmacological Category

Anti-inflammatory

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

12 mg, 25 mg, 75 mg or 100 mg deracoxib

H. How Supplied

Tablets are available as 12 mg, 25 mg, 75 mg and 100 mg round, brownish, half-scored tablets in 7, 30 and 90 count bottles.

I. Dispensing Status

Rx

J. Dosage Regimen

Osteoarthritis Pain and Inflammation: 0.45-0.91 mg/lb/day (1 to 2 mg/kg/day) as a single dose, as needed. Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets.

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. Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to

provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets.

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. The first dose should be given approximately 1 hour prior to dental surgery and subsequent doses should be given daily for up to two additional treatments. Dogs needing a dose of less than 12.5 mg can only be accurately dosed through use of the 12 mg tablet, which can be broken in half to provide 6 mg. Do not attempt to accurately dose smaller dogs through the use of breaking larger tablets.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

Doxidyl™ Chewable Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Doxidyl™ Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs.

Doxidyl™ Chewable Tablets are indicated for the control of postoperative pain and inflammation associated with dental surgery in dogs.

N. Reference Listed New Animal Drug

Deramaxx™; deracoxib; NADA 141-203; Elanco US Inc.

II. BIOEQUIVALENCE

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTA) of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug (RLNAD)). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

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 available in 12, 25, 75 and 100 mg tablet sizes. The *in vivo* blood level study was conducted in 24 healthy intact female beagles at least one year of age and weighing between 14.8 and 18.3 pounds. Bioequivalence was demonstrated between the 25 mg RLNAD deracoxib chewable tablet and the 25 mg generic deracoxib chewable tablet by demonstrating that the confidence limits for the difference between the pivotal parameters C_{MAX} and AUC are contained within the equivalence limits of 80% and 125%. There were no serious adverse events recorded during the study. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 12 mg, 75 mg and 100 mg chewable tablets was

requested. Comparative dissolution study data was used to demonstrate that the generic 12 mg, 75 mg and 100 mg deracoxib chewable tablets are comparable to the generic 25 mg deracoxib chewable tablet used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 12 mg, 75 mg and 100 mg chewable tablets was granted. The study information is summarized below.

A. Canine Blood-level Bioequivalence Study

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

Study Title: The Bioequivalence of Two Deracoxib Formulations in Dogs, SBL 017-01565.

Study Dates: June 14, 2017 to October 26, 2017

Study Locations:

Analytical test facility: Middleton, Wisconsin, United States

In-life test facility: Las Cruces, New Mexico, United States

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of generic sponsor's 25 mg generic Doxidyl™ (deracoxib) chewable tablet and the RLNAD 25 mg Deramaxx™ (deracoxib) chewable tablet in a randomized, two-period, two-treatment, two-sequence crossover study in dogs using Good Laboratory Practices for Nonclinical Laboratory Studies standards.

Study Animals: 24 healthy intact female beagles at least one year of age and weighing between 14.8 and 18.3 pounds.

Experimental Design: A randomized, two period, two treatment, two sequence crossover study to evaluate the relative bioavailability of a generic 25 mg chewable tablet formulation of Doxidyl™ (deracoxib) compared to an equivalent dose of the RLNAD Deramaxx™ (deracoxib) chewable tablet (Elanco US, Inc., NADA 141-203) in 24 healthy intact female beagles at least one year of age and weighing between 14.8 and 18.3 pounds.

Drug Administration: One 25 mg test or reference tablet was administered to each test animal in a two-sequence cross-over study.

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. All animals remained healthy during the study. No adverse events were recorded.

Statistical Methods: The study was conducted as a randomized two-period, two-treatment, two-sequence crossover design with a 14-day washout time between

periods. 24 female dogs were enrolled in the study and sequence assignment was done completely at random. Primary variables evaluated were area under the curve from time 0 to the first observed concentration below the limit of quantitation (AUC) and maximum concentration (C_{MAX}). Time to maximum concentration (T_{MAX}) was also evaluated.

Prior to analysis AUC and C_{MAX} were transformed using the natural logarithmic transformation. Ninety percent confidence intervals about the difference of in the means for the logarithmically transformed variables (test - reference) were estimated. The endpoints for the confidence interval were back-transformed to geometric means. For the two products to be considered bioequivalent, the back-transformed confidence bounds for both AUC and C_{MAX} must fall between 80% and 125%.

Results: As seen in Table I.1 below, the bioequivalence criterion is met for both AUC and C_{MAX} and we can conclude that bioequivalence has been established between Provetica AH LLC's chewable tablet formulation of deracoxib (test) and Elanco Animal Health's DeramaxxTM chewable tablet (reference).

Table I.1: Bioequivalence Evaluation in Dogs

Parameter	Test	Reference	Ratio*	Ratio Lower Bound (%)	Ratio Upper Bound (%)
AUC (ppm*h)	7807.97†	7809.53†	99.98	88.79	112.58
C_{MAX} (ppm)	908.78†	911.51†	99.70	86.66	114.70
T_{MAX} (h)	1.98‡	2.08‡	NE	NE	NE

* Ratio = Test/Reference

† Geometric mean

‡ Arithmetic mean

NE = not estimated

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: Bioequivalence between the 25 mg generic DoxidyTM (deracoxib) chewable tablet (test) and the 25 mg RLNAD DeramaxxTM (deracoxib) chewable tablet (reference) has been established in the *in vivo* bioequivalence study.

B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg deracoxib chewable tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 12 mg, 75 mg and 100 mg tablets was requested. To qualify for a biowaiver for each of these product strengths, comparative dissolution studies were conducted to determine the dissolution profiles of Provetica AH LLC's generic 12 mg, 25 mg, 75 mg, and 100 mg deracoxib tablets. The similarity factor (f2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 12 mg and generic 25 mg tablets
- Generic 75 mg and generic 25 mg tablets
- Generic 100 mg and generic 25 mg tablets

Dissolution parameters:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.4% Tween-20 in water
- Dissolution medium volume: 1000 mL (12 mg and 25 mg), 2000 mL (75 mg and 25 mg) and 4000 mL (100 mg and 25 mg)
- Temperature: 37 °C
- Paddle speed: 75 rpm
- Data points: 10, 30, 45, 60 and 90 minutes

The biolot 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 similarity factor (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 the following table:

Table II.2. Calculated f_2 values

	Generic 12 mg tablet	Generic 75 mg tablet	Generic 100 mg tablet
Generic 25 mg tablet	$f_2 = 67.5$	$f_2 = 57.4$	$f_2 = 60.1$

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 12 mg, 75 mg and 100 mg deracoxib chewable tablets is granted.

III. EFFECTIVENESS

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in dogs, which are not food producing animals.

VI. USER SAFETY

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Doxidyl™:

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.

VII. AGENCY CONCLUSIONS

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that Doxidyl™, when used according to the label, is safe and effective.