

Date of Approval: July 7, 2021

FREEDOM OF INFORMATION SUMMARY
ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-703
Carprofen Tablets
Dogs

For the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

Sponsored by:
Dechra Veterinary Products LLC

Executive Summary

Carprofen Tablets (carprofen tablets) are approved to relieve pain and inflammation associated with osteoarthritis in dogs; and to control postoperative pain associated with both soft tissue and orthopedic surgeries in dogs. Carprofen Tablets are a generic version of RIMADYL®.

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Carprofen Tablets	carprofen tablets	Abbreviated New Animal Drug Application (ANADA) 200-703	Dechra Veterinary Products LLC
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	RIMADYL®	carprofen tablets	New Animal Drug Application (NADA) 141-053	Zoetis Inc.

Carprofen is in the propionic acid class of non-narcotic, nonsteroidal anti-inflammatory drugs (NSAIDs) and has characteristic analgesic and antipyretic activity. Like many NSAIDs, carprofen 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.

This sponsor produces a generic carprofen in both flavored and unflavored tablets which differ only in that the flavoring is removed to manufacture the unflavored tablets. To support the approval of unflavored Carprofen Tablets, the sponsor conducted one *in vivo* blood-level study in fasted dogs to show that the flavored 25 mg Carprofen Tablets are bioequivalent to the RLNAD, along with dissolution data comparing the dissolution profiles for the flavored tablets to the unflavored tablets. No serious adverse events were reported during the study.

The sponsor conducted comparative *in vitro* dissolution studies comparing the dissolution profiles for the unflavored 25, 75 mg, and 100 mg Carprofen Tablets to

the dissolution profile for the approved flavored 25 mg Carprofen Tablet. The flavored 25 mg Carprofen Tablet was used as the comparator because it was shown to be bioequivalent to the RLNAD in the *in vivo* blood-level study. Because all strengths of unflavored Carprofen Tablets had similar dissolution profiles to the flavored 25 mg Carprofen Tablet, the unflavored 25 mg, 75 mg, and 100 mg Carprofen Tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). Therefore, FDA granted a biowaiver for all strengths of unflavored Carprofen Tablets.

Conclusions

Based on the data submitted by the sponsor for the approval of Carprofen 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 200-703

B. Sponsor

Dechra Veterinary Products LLC
7015 College Blvd
Suite 525
Overland Park, KS 66211

Drug Labeler Code: 017033

C. Proprietary Name

Carprofen Tablets

D. Drug Product Established Name

carprofen tablets

E. Pharmacological Category

Non-steroidal anti-inflammatory drug (NSAID)

F. Dosage Form

Caplet

G. Amount of Active Ingredient

25, 75, or 100 mg carprofen per caplet

H. How Supplied

Each caplet size is scored and packaged in bottles containing 30, 60, or 180 caplets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The recommended dosage for oral administration to dogs is 2 mg/lb (4.4 mg/kg) of body weight daily. The total daily dose may be administered as 2 mg/lb of body weight daily or divided and administered as 1 mg/lb (2.2 mg/kg) twice daily. For the control of postoperative pain, administer approximately 2 hours before the procedure.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

Carprofen Tablets are indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs.

N. Reference Listed New Animal Drug

Rimadyl®; carprofen tablets; NADA 141-053; Zoetis 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 along with a dissolution study comparing the unflavored generic tablets to the flavored generic tablets were conducted to demonstrate product bioequivalence. This sponsor produces a generic carprofen in both flavored and unflavored tablets which differ only in that the flavoring is removed to manufacture the unflavored generic tablets. Because removal of flavoring from a formulation would not be expected to impact bioavailability, the *in vivo* data using the sponsor's flavored generic tablet was suitable to demonstrate *in vivo* bioequivalence between the generic 25 mg formulation (regardless of flavor) and the 25 mg RLNAD tablet. The *in vivo* study used the sponsor's approved formulation for a 25 mg flavored generic tablet, under ANADA 200-681, and the 25 mg RLNAD. The RLNAD is available in 25, 75, and 100 mg caplet sizes.

The *in vivo* blood-level study was conducted in 24 healthy, fasted beagle 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 caplets and the flavored generic tablets by the average bioequivalence approach as described in the Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the unflavored generic 25 mg, 75 mg, and 100 mg tablets was requested. Dissolution data was used to demonstrate that the unflavored generic 25 mg, 75 mg, and 100 mg carprofen tablets are comparable to the flavored generic 25 mg tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the unflavored generic 25 mg, 75 mg, and 100 mg carprofen 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 flavored generic carprofen tablets and the RLNAD tablets.

Title: Pivotal Two-Way Oral Bioequivalence Study of Carprofen (Flavored Tablets) in Beagles (Study No. 017-01604).

Study Dates: March 7, 2018 to November 14, 2018

Study Location:

In-life phase: Las Cruces, NM

Bioanalytical testing: Colorado Springs, CO

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the flavored generic 25 mg carprofen tablets and the RLNAD in fasted dogs.

Study Animals: 24 intact (non-pregnant) female beagle dogs between 2 and 8 years of age and weighing from 9 to 14 kg on the day of initial dose administration (study day 0).

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study. The study was conducted according to Good Laboratory Practices (GLP) regulations.

Drug Administration: Each animal received 25 mg of either the generic or RLNAD carprofen tablets according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of carprofen 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 dogs with a 14-day washout between periods. Appropriate randomization of animals 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 random effects of subject nested within sequence. Prior to 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, both 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	371155 [†]	360234 [†]	1.03	0.98	1.09
C _{MAX} (ng/mL)	45492 [†]	45510 [†]	1.00	0.92	1.09
T _{MAX} (hour) (SD [‡])	1.32 (0.83) [‡]	1.57 (1.21) [‡]	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 flavored generic 25 mg carprofen tablets and the RLNAD 25 mg carprofen tablets are bioequivalent in dogs.

B. Bioequivalence Waiver

A pivotal *in-vivo* blood-level bioequivalence study was conducted using the flavored 25 mg carprofen tablet strength. A biowaiver for the unflavored generic 25 mg, 75 mg and 100 mg 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 unflavored generic 25 mg, 75 mg, and 100 mg carprofen. The similarity factor (f₂) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Flavored generic 25 mg tablets and unflavored generic 25 mg tablets
- Flavored generic 25 mg tablets and unflavored generic 75 mg tablets
- Flavored generic 25 mg tablets and unflavored generic 100 mg tablets

The objective was to satisfy f₂ criteria between the flavored generic 25 mg tablet strength and the unflavored generic 25 mg, 75 mg, and 100 mg tablet strengths. The analytical method and dissolution conditions were the same as documented under A 200-681. The dissolution conditions were as follows:

Apparatus: USP Method 2 (paddles)

Speed: 50 rpm

Medium: 50 mM phosphate buffer, pH 7.5

Media Volume: 900 mL
Temperature: 37 °C + 0.5 °C
Pull Time for profile: 10, 15, and 30 minutes
Pull Volume: 10 mL

The flavored 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.

In all cases the unflavored generic carprofen tablets dissolved $\geq 85\%$ in less than 15 minutes, therefore 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. The dissolution data demonstrates that all strengths of the unflavored carprofen tablets are the same as the flavored 25 mg tablet and bioequivalent to the RLNAD. Therefore, a biowaiver for the unflavored generic 25 mg, 75 mg, and 100 mg strengths of the carprofen 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 Carprofen Tablets:

Keep out of reach of children. Not for human use. Consult a physician in cases 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 Carprofen Tablets, when used according to the label, is safe and effective for the indications listed in Section I.M. above.