

Date of Approval: July 29, 2020

# **FREEDOM OF INFORMATION SUMMARY**

## **ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION**

**ANADA 200-687**  
**Carprofen Chewable Tablets**  
**(carprofen)**  
**Dogs**

Carprofen Chewable 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.

**Sponsored by:**  
**Cronus Pharma Specialities India Private Ltd.**

## Executive Summary

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

	Proprietary Name	Established Name	Application Type and Number	Sponsor
<b>Generic Animal Drug</b>	Carprofen Chewable Tablets	Carprofen	ANADA <sup>a</sup> 200-687	Cronus Pharma Specialities India Private Ltd.
<b>Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)</b>	Rimadyl®	Carprofen	NADA <sup>b</sup> 141-111	Zoetis Inc.
<sup>a</sup> <a href="#">Abbreviated New Animal Drug Application</a> for a generic animal drug. <sup>b</sup> <a href="#">New Animal Drug Application</a> for a brand name animal drug.				

## 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.

For this approval, FDA approved a suitability petition submitted by the sponsor that requested permission to submit an approval application for a generic animal drug that differed in strength and scoring from the RLNAD. Carprofen Chewable Tablets are 25 mg, 50 mg, 75 mg, and 100 mg strength scored tablets; the 37.5 mg strength tablet is unscored. Rimadyl® Chewable Tablets, the RLNAD, are 25 mg, 75 mg, and 100 mg strength scored tablets.

The sponsor conducted one *in vivo* blood-level study to show that the 25 mg Carprofen Chewable Tablets are bioequivalent to the 25mg Rimadyl® Chewable Tablets. No serious adverse events were recorded during the study. The sponsor also conducted comparative *in vitro* dissolution studies to show that the dissolution profiles for the 37.5 mg, 50 mg, 75 mg and 100 mg Carprofen Chewable Tablets were similar to the dissolution profile for the 25 mg Carprofen Chewable Tablets. Because all strengths had similar dissolution profiles, the 37.5 mg, 50 mg, 75 mg, and 100 mg tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). Therefore, FDA granted a biowaiver for these strengths.

### **Conclusions**

Based on the data submitted by the sponsor for the approval of Carprofen Chewable Tablets, 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.....	10
V. AGENCY CONCLUSIONS.....	10

**I. GENERAL INFORMATION**

**A. File Number**

ANADA 200-687

**B. Sponsor**

M/s. Cronus Pharma Specialities India Private Limited  
Sy No-99/1, GMR Hyderabad Aviation SEZ Limited  
Mamidipalli Village, Shamshabad Mandal,  
Ranga Reddy, Hyderabad  
Telangana 501218, India

Drug Labeler Code: 069043

U.S. Agent Name and Address:  
Ms. Melanie Archer  
Cronus Pharma LLC  
2 Tower Center Boulevard  
Suite 1101A  
East Brunswick, NJ 08816

**C. Proprietary Name**

Carprofen Chewable Tablets

**D. Drug Product Established Name**

carprofen

**E. Pharmacological Category**

Non-steroidal anti-inflammatory drug (NSAID)

**F. Dosage Form**

Chewable tablet

**G. Amount of Active Ingredient**

25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg of carprofen per tablet

**H. How Supplied**

Carprofen Chewable Tablets are scored (except for the unscored 37.5 mg strength), and contain 25 mg, 37.5 mg, 50 mg, 75 mg, or 100 mg of carprofen per tablet. Each tablet size is packaged in bottles containing 60 or 180 tablets.

**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 once 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. For scored tablets, dosage should be calculated in half-tablet increments.

## **K. Route of Administration**

Oral

## **L. Species/Class**

Dogs

## **M. Indications**

Carprofen Chewable 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 (RLNAD)**

Rimadyl®; carprofen; NADA 141-111; Zoetis 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 certain dosage forms, the agency will grant a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

The sponsor submitted a suitability petition (FDA-2018-P-2407) requesting permission to submit an ANADA for a generic new animal drug that differed in strength and scoring from the RLNAD. The proposed generic new animal drug is a chewable tablet containing 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg of carprofen per tablet. The 25 mg, 50 mg, 75 mg, and 100 mg strength tablets will be scored, while the 37.5 mg strength tablet will be unscored. The RLNAD is a chewable tablet containing 25 mg, 75 mg, and 100 mg of carprofen per tablet. All RLNAD tablet strengths are scored. This petition was approved on November 09, 2018, under 512(n)(3)(C) of the FD&C Act.

For this ANADA, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD carprofen 25 mg chewable tablets. The RLNAD is available in 25, 75, and 100 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 36 healthy, fasted male beagle dogs. There were no serious adverse events reported during the study. 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 Rimadyl® (carprofen) Chewable Tablets and the 25 mg generic Carprofen Chewable Tablets by the average bioequivalence approach as described in Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 37.5 mg, 50 mg, 75 mg and 100 mg chewable tablets was requested. Dissolution data was used to demonstrate that the generic 37.5 mg, 50 mg, 75 mg and 100 mg carprofen chewable tablets are comparable to the generic 25 mg chewable tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 37.5 mg, 50 mg, 75 mg and 100 mg carprofen 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 carprofen chewable tablets (25 mg).

**Title:** Plasma Bioavailability Study of Test Carprofen Chewable Tablets and Reference Article Rimadyl® (carprofen) Chewable Tablets Administered Orally in the Dog (Study No. TH180069 (in-life facility); AB/BA/011-18 (bioanalytical facility))

**Study Dates:** August 16, 2018 to December 28, 2018

#### **Study Locations:**

In-life phase: Terre Haute, IN

Bioanalytical testing: Andhra Pradesh, India

#### **Study Design:**

**Objective:** The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of the generic 25 mg Carprofen Chewable Tablets and the RLNAD 25 mg Rimadyl® (carprofen) Chewable Tablets in a randomized, two-period, two-sequence, single-dose crossover study in dogs.

**Study Animals:** 36 male intact beagle dogs, 9 – 60 months of age, 8.56 – 11.375 kg

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

**Drug Administration:** Each animal received 25 mg of either the generic or RLNAD carprofen chewable tablet 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 36 male beagle dogs with a seven-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 <sup>◇</sup>	Lower 90% CI	Upper 90% CI
AUC (µg/mL)*hour	136.26 <sup>†</sup>	133.62 <sup>†</sup>	1.0198	95.33	109.09
$C_{MAX}$ (µg/mL)	22.52 <sup>†</sup>	22.41 <sup>†</sup>	1.0047	95.66	105.51
$T_{MAX}$ (hours) (SD <sup>‡</sup> )	1.15 (0.43) <sup>‡</sup>	1.09 (0.74) <sup>‡</sup>	NE	NE	NE

<sup>†</sup> Geometric mean

<sup>‡</sup> Arithmetic mean and standard deviation (SD)

<sup>◇</sup> Ratio = Generic:RLNAD

CI = confidence interval

NE = not estimated

## B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg carprofen chewable tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 37.5 mg, 50 mg, 75 mg, and 100 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 37.5 mg, 50 mg, 75 mg, and 100 mg carprofen chewable tablets. The similarity factor ( $f_2$ ) calculation was used



to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 25 mg and generic 37.5 mg tablets
- Generic 25 mg and generic 50 mg tablets
- Generic 25 mg and generic 75 mg tablets
- Generic 25 mg and generic 100 mg tablets

The objective was to satisfy  $f_2$  criteria between the generic 25 mg chewable tablet strength and the generic 37.5 mg, 50 mg, 75 mg, and 100 mg chewable tablet strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II (paddle) with peak vessel
- Dissolution medium: Phosphate buffer, pH  $7.5 \pm 0.05$
- Dissolution medium volume: 900 mL
- Temperature:  $37^\circ\text{C} \pm 0.5^\circ\text{C}$
- Paddle speed: 50 rpm
- Number of vessels: 12
- Data points: 10, 15, 30, 45, and 60 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 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 Table II.2 below:

**Table II.2. Similarity ( $f_2$ ) Results**

	Generic 37.5 mg chewable tablet	Generic 50 mg chewable tablet	Generic 75 mg chewable tablet	Generic 100 mg chewable tablet
Generic 25 mg chewable tablet	$f_2 = 96.87$	$f_2 = 96.87$	$f_2 = 72.15$	$f_2 = 78.36$

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 37.5 mg, 50 mg, 75 mg, and 100 mg 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 Carprofen Chewable Tablets:

**Warnings:** Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans.

#### **V. AGENCY CONCLUSIONS**

This information submitted in support of this ANADA satisfies the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Carprofen Chewable Tablets when used according to the label, is safe and effective.