

Date of Approval: June 28, 2021

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION**

**ANADA 200-706**

**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:**

**Felix Pharmaceuticals Pvt. Ltd.**

**Executive Summary**

Carprofen Chewable 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 Chewable Tablets are a generic version of RIMADYL®.

	<b>Proprietary Name</b>	<b>Established Name</b>	<b>Application Type and Number</b>	<b>Sponsor</b>
<b>Generic Animal Drug</b>	Carprofen Chewable Tablets	carprofen	Abbreviated New Animal Drug Application (ANADA) 200-706	Felix Pharmaceuticals Pvt. Ltd
<b>Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)</b>	RIMADYL®	carprofen	New Animal Drug Application (NADA) 141-111	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.

The sponsor conducted one *in vivo* blood-level study in fasted dogs to show that the 25 mg Carprofen Chewable Tablets are bioequivalent to the 25 mg RIMADYL® tablets. No serious adverse events were reported during the study.

The sponsor also conducted comparative *in vitro* dissolution studies comparing the dissolution profiles for the 75 mg and 100 mg generic tablets to the dissolution profile for the 25 mg generic tablet. The 25 mg generic tablet was used as the comparator because it was shown to be bioequivalent to the 25 mg RIMADYL® tablet in the *in vivo* blood-level study. Because all strengths had similar dissolution profiles, the 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.

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**I. GENERAL INFORMATION**

**A. File Number**

ANADA 200-706

**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**

CARPROFEN Chewable Tablets

**D. Drug Product Established Name**

carprofen

**E. Pharmacological Category**

Non-steroidal anti-inflammatory drug

**F. Dosage Form**

Chewable tablet

**G. Amount of Active Ingredient**

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

**H. How Supplied**

Each tablet size is scored and packaged in bottles containing 30, 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. Indication(s)**

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**

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 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 approved in 25, 75, and 100 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 28 healthy, fasted dogs. The pivotal parameters to evaluate bioequivalence are the observed maximum plasma drug concentration (C<sub>MAX</sub>) and area under the concentration-time curve (AUC) from time 0 minutes to the last sampling time before the first unquantifiable concentration after C<sub>MAX</sub>. Bioequivalence was demonstrated for carprofen between the 25 mg RLNAD and the 25 mg generic 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 generic 75 mg and 100 mg tablets was requested. Dissolution data was used to demonstrate that the generic 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 75 mg and 100 mg carprofen tablet sizes was granted. The study information is summarized below.

## A. Blood-level Bioequivalence Study in Dogs

**Title:** Pivotal Bioequivalence Study of RIMADYL® Chewable Tablets and a Generic Formulation of Carprofen when Administered Orally to Beagle Dogs (Study No: 080-BC-4616)

**Study Dates:** July 24, 2018 to November 28, 2018

### Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Ontario, Canada

### Study Design:

**Objective:** To assess the pharmacokinetics and bioequivalence of test article (generic carprofen chewable tablets) compared to the RLNAD in dogs using a two-period, two-sequence crossover design.

**Study Animals:** 28 intact male dogs, aged 17 months to 31 months and weighing between 10 – 13 kg.

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

**Drug Administration:** Each animal received 25 mg of either the generic or RLNAD carprofen 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 Method:

The laboratory study was conducted as a randomized, masked, two-period, two-sequence, two-treatment, single-dose crossover design using 28 dogs with a 7-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<sub>MAX</sub> and AUC fall within the prescribed bounds (Table II.1 ). The mean values of T<sub>MAX</sub> obtained for the generic article and RLNAD were summarized

Parameter	Generic Mean	RLNAD Mean	Ratio <sup>◇</sup>	Lower 90% CI	Upper 90% CI
AUC (µg/mL)*minute	9975 <sup>†</sup>	10003 <sup>†</sup>	1.0	0.95	1.05
C <sub>MAX</sub> (µg/mL)	19.2 <sup>†</sup>	20.7 <sup>†</sup>	0.93	0.88	0.97
T <sub>MAX</sub> (minute)	71.79	57.86	NE	NE	NE

<sup>†</sup> Geometric mean

<sup>◇</sup> Ratio = Generic/Reference

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 25 mg Carprofen Chewable Tablets and the RLNAD are bioequivalent in dogs.

**B. Bioequivalence Waiver**

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg generic tablet strength. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 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 the generic 25 mg, 75 mg, and 100 mg carprofen tablets. The similarity factor (f<sub>2</sub>) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

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

The objective was to satisfy f<sub>2</sub> criteria between the generic 25 mg tablet strength and the generic 75 mg and generic 100 mg carprofen tablets.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: Phosphate buffer
- pH 7.5
- Dissolution medium volume: 900 mL
- Temperature: 37 ± 0.5 °C
- Paddle speed: 75 rpm
- Number of vessels: 12
- Data points: 10, 15, 30, 45, 60, and 90 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 one of the 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 Results**

<b>Dissolution Comparison</b>	<b>Similarity Results (<math>f_2</math>)</b>
25 mg generic to the 75 mg generic	58.7
25 mg generic to the 100 mg generic	52.6

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

**Warnings:** Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

### **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 Chewable Tablets, when used according to the label, is safe and effective for the indications listed in Section I.M. above.