Date of Approval: January 12, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-733

Marbofloxacin Chewable Tablets

(marbofloxacin)

Dogs and Cats

Marbofloxacin Chewable Tablets are indicated for the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin.

Sponsored by:

Felix Pharmaceuticals Pvt. Ltd.

Executive Summary

Marbofloxacin Chewable Tablets are approved for the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin. Marbofloxacin Chewable Tablets are a generic version of Zeniquin® tablets.

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Marbofloxacin Chewable Tablets	marbofloxacin	Abbreviated New Animal Drug Application (ANADA) 200-733	Felix Pharmaceuticals Pvt. Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	Zeniquin®	marbofloxacin	New Animal Drug Application (NADA) 141-151	Zoetis Inc.

Marbofloxacin, a fluoroquinolone antibiotic, has bactericidal activity against a broad range of gram-negative and gram-positive bacteria. When administered orally to fasted animals, marbofloxacin is rapidly and almost completely absorbed from the gastrointestinal tract, penetrating tissues and body fluids.

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 50 mg Marbofloxacin Chewable Tablets are bioequivalent to the 50 mg Zeniquin® tablets. The sponsor also conducted one *in vivo* blood-level study in fasted cats to show that the 25 mg Marbofloxacin Chewable Tablets are bioequivalent to the 25 mg Zeniquin® tablets. No serious adverse events were reported during either study.

Zeniquin® tablets are available in 25 mg, 50 mg, 100 mg, and 200 mg tablet sizes. All four strengths are labeled for dogs. Only the 25 mg strength is labeled for cats. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 25 mg, 100 mg, and 200 mg chewable tablets in dogs was requested. To qualify for a biowaiver for each of these product strengths in dogs, a comparative *in vitro* dissolution study was conducted to determine the dissolution profiles of generic and RLNAD tablets of all strengths. Dissolution data was used to demonstrate that the generic 25 mg, 50 mg, 100 mg, and 200 mg Marbofloxacin Chewable Tablets are comparable to the RLNAD 25 mg, 50 mg, 100 mg, and 200 mg Zeniquin® (marbofloxacin) tablets, respectively. Therefore, a

biowaiver for the generic 25 mg, 100 mg, and 200 mg Marbofloxacin Chewable Tablets in dogs was granted.

User Safety
The labeling for Marbofloxacin Chewable Tablets includes a warning that people who have a history of hypersensitivity to fluoroquinolones should avoid the drug. The labeling also includes a warning about the risk of photosensitization in people after excessive exposure to quinolones.

Conclusions
Based on the data submitted by the sponsor for the approval of Marbofloxacin Chewable Tablets, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

ANADA 200-733

B. Sponsor

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

Drug Labeler Code: 086101

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

C. Proprietary Name

Marbofloxacin Chewable Tablets

D. Drug Product Established Name

marbofloxacin

E. Pharmacological Category

Antimicrobial

F. Dosage Form

chewable tablet

G. Amount of Active Ingredient

25 mg, 50 mg, 100 mg, or 200 mg marbofloxacin per tablet

H. How Supplied

25 mg scored tablets supplied in bottles containing 100 tablets or 250 tablets
50 mg scored tablets supplied in bottles containing 100 tablets or 250 tablets
100 mg scored tablets supplied in bottles containing 50 tablets
200 mg scored tablets supplied in bottles containing 50 tablets

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The recommended dosage for oral administration to dogs and cats is 1.25 mg marbofloxacin per lb of body weight once daily, but the dosage may be safely increased to 2.5 mg/lb.

For the treatment of skin and soft tissue infections, Marbofloxacin Chewable Tablets should be given for 2-3 days beyond the cessation of clinical signs for a maximum of 30 days. For the treatment of urinary tract infections, Marbofloxacin Chewable Tablets should be administered for at least 10 days. If no improvement is noted within 5 days, the diagnosis should be re-evaluated and a different course of therapy considered.

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indications

Marbofloxacin Chewable Tablets are indicated for the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin.

N. Reference Listed New Animal Drug

Zeniquin®; marbofloxacin; NADA 141-151; 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.

The sponsor submitted a suitability petition (FDA-2018-P-1351) requesting permission to submit an ANADA for a generic new animal drug that differed in dosage form from the RLNAD. The RLNAD is a compressed tablet while the generic product is a compressed chewable tablet. This petition was approved on June 7, 2018, under 512(n)(3)(C) of the FD&C Act.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD marbofloxacin 50 mg tablets in dogs and the 25 mg tablets in cats. The RLNAD is available in 25 mg, 50 mg, 100 mg, and 200 mg tablet sizes. One *in vivo* blood-level study was conducted using the 50 mg tablet size 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 50 mg Zeniquin® (marbofloxacin) tablets and the 50 mg Marbofloxacin Chewable Tablets by the average bioequivalence approach as described in the Statistical Methods section below. One *in vivo* blood-level study was conducted using the 25 mg tablet size in 24 healthy, fasted cats. The pivotal parameters to evaluate bioequivalence are C_{MAX} and AUC from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX}. Bioequivalence was demonstrated between the 25 mg Zeniquin® (marbofloxacin) tablets and the 25 mg Marbofloxacin Chewable Tablets by the average bioequivalence approach as described in the Statistical Methods section below. A biowaiver for the generic 25 mg, 100 mg, and 200 mg chewable tablets in dogs was requested. Dissolution data was used to demonstrate that the generic 25 mg, 50 mg, 100 mg, and 200 mg Marbofloxacin Chewable Tablets are comparable to the RLNAD 25 mg, 50 mg, 100 mg, and 200 mg Zeniquin® (marbofloxacin) tablets, respectively. Therefore, a biowaiver for the generic 25 mg, 100 mg, and 200 mg Marbofloxacin Chewable Tablets in dogs was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of Zeniquin® and a Generic Formulation of Marbofloxacin Chewable Tablets when Administered Orally to Beagle Dogs (Study No. 080-BC-2619).

Study Dates: May 15, 2020 to June 13, 2020

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 50 mg Marbofloxacin Chewable Tablets and the RLNAD 50 mg Zeniquin® (marbofloxacin) in fasted dogs.

Study Animals: Twenty-four healthy intact male dogs, aged 19 – 53 months and weighing 11.3 – 14.0 kg.

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

Drug Administration: Each animal received 50 mg of either the generic or RLNAD marbofloxacin according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of marbofloxacin 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 healthy male 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_{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	33044†	32364†	1.02	1.00	1.04
C_{MAX} (ng/mL)	2846†	2621†	1.09	1.04	1.14
T_{MAX} (hours) (SD‡)	1.11 (0.30)‡	1.42 (0.38)‡	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 generic 50 mg Marbofloxacin Chewable Tablets and the RLNAD 50 mg Zeniquin® (marbofloxacin) tablets are bioequivalent in dogs.

B. Blood-level Bioequivalence Study in Cats

Title: Pivotal Bioequivalence Study of Zeniquin® and a Formulation of Generic Marbofloxacin Chewable Tablets when Administered Orally to Cats (Study No. 080-BF-2719).

Study Dates: October 5, 2020 to November 13, 2020

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 25 mg Marbofloxacin Chewable Tablets and the RLNAD 25 mg Zeniquin® (marbofloxacin) in fasted cats.

Study Animals: Twenty-four healthy neutered male cats, aged 1 – 5 years and weighing 4.9 – 6.2 kg.

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

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

Measurements and Observations: The plasma concentrations of marbofloxacin 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 healthy male cats 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. 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.2). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.2. Bioequivalence Evaluation

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	40255†	39786†	1.01	0.97	1.06
C_{MAX} (ng/mL)	2865†	2903†	0.99	0.91	1.07
T_{MAX} (hours) (SD‡)	2.13 (1.88)‡	2.43 (2.08)‡	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 generic 25 mg Marbofloxacin Chewable Tablets and the RLNAD 25 mg Zeniquin® (marbofloxacin) tablets are bioequivalent in cats.

C. **Bioequivalence Waiver**

Two pivotal *in vivo* blood bioequivalence studies were conducted using the 25 mg marbofloxacin tablets in cats and the 50 mg marbofloxacin tablets in dogs. A biowaiver for the generic 25 mg, 100 mg, and 200 mg chewable tablets in dogs 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 and RLNAD 25 mg, 50 mg, 100 mg, and 200 mg marbofloxacin 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 RLNAD 25 mg tablets
- Generic 50 mg and RLNAD 50 mg tablets
- Generic 100 mg and RLNAD 100 mg tablets
- Generic 200 mg and RLNAD 200 mg tablets

The objective was to satisfy f_2 criteria between the generic 25, 50, 100 and 200 mg chewable tablet strengths and the RLNAD 25, 50, 100 and 200 mg tablet strengths.

Test conditions were as follows:
- Dissolution apparatus: USP Apparatus I (Basket, 10 Mesh)
- Dissolution medium: 0.1 N HCl
- Dissolution medium volume: 900 mL
- Temperature: 37 °C ± 5 °C
- Paddle speed: 100 rpm
- Number of vessels: 12

- Data points: 15, 20, 30, 45, 60, and 75 minutes

The generic drug lot numbers used in the *in vivo* bioequivalence studies (dogs and cats) were the same lots 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.3 below:

Table II.3. Similarity Results

Dissolution Comparison	Similarity Results
25 mg generic to the 25 mg RLNAD	66
50 mg generic to the 50 mg RLNAD	55
100 mg generic to the 100 mg RLNAD	60
200 mg generic to the 200 mg RLNAD	60

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 25 mg, 100 mg, and 200 mg marbofloxacin chewable tablets in dogs is granted.

III. HUMAN FOOD SAFETY

This drug is intended for use in dogs and cats. 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 Marbofloxacin Chewable Tablets:

For use in animals only. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to fluoroquinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

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 Marbofloxacin Chewable

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