Date of Approval: January 13, 2023

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-736

Marbofloxacin

Tablets

Dogs and Cats

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

Sponsored by:

ZYVET AH, Inc.

Executive Summary

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

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Marbofloxacin	marbofloxacin	Abbreviated New Animal Drug Application (ANADA) 200-736	ZYVET AH, Inc.
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 fluroquinolone 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 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 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 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 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 tablets in dogs was granted.

User Safety
The labeling for Marbofloxacin tablets includes a warning that people who have a history of hypersensitivity to fluroquinolones 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 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 200-736

B. Sponsor

ZYVET AH, Inc.
73 Route 31N
Pennington, NJ 08534

Drug Labeler Code: 086117

C. Proprietary Name

Marbofloxacin

D. Drug Product Established Name

marbofloxacin

E. Pharmacological Category

Antimicrobial

F. Dosage Form

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 a bottle containing 50 tablets
200 mg scored tablets supplied in a bottle 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 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 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. Indication

Marbofloxacin 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.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD marbofloxacin 50 mg tablet in dogs and 25 mg tablet in cats. The RLNAD is available in 25, 50, 100, and 200 mg tablet sizes. One *in vivo* blood-level study was conducted using the 50 mg tablet in 18 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 RLNAD marbofloxacin tablet and the 50 mg generic marbofloxacin tablet in dogs 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 in 18 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 RLNAD marbofloxacin tablet and the 25 mg generic marbofloxacin tablet in cats 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 tablets in dogs was requested. Dissolution data was used to demonstrate that the generic 100 mg and 200 mg marbofloxacin tablets are comparable to the generic 50 mg tablet strength used in the dog *in vivo* blood-level bioequivalence study. In addition, dissolution data was used to demonstrate that the generic 25 mg marbofloxacin tablet is comparable to the RLNAD 25 mg tablet strength. Therefore, a biowaiver for the generic 25 mg, 100 mg,

and 200 mg marbofloxacin tablets in dogs was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: Blood-level Bioequivalence Study in Dogs: A masked, Balanced, Randomized, Two Period, Two Sequence, Single Oral Dose, Cross Over Bioequivalence Study of Marbofloxacin Tablet 50 mg and Zeniquin® Tablet 50 mg in Healthy Adult Dogs Under Fasting Conditions (Study No. 3118-0003).

Study Dates: May 17, 2021 to February 22, 2022

Study Locations:

In-life phase: Mattawan, Michigan

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 tablets and the RLNAD 50 mg Zeniquin® (marbofloxacin) tablets in fasted dogs.

Study Animals: Eighteen male dogs between the ages of 9 months and 3 years and weighing 8.4-10.7 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 tablets 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 18 dogs with a 10-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	36452†	36290†	1.004	0.966	1.045
C_{MAX} (ng/mL)	3022†	3065†	0.986	0.949	1.025
T_{MAX} (hours) (SD)‡	1.04 (0.30)‡	1.16 (0.36)‡	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 tablet and the RLNAD 50 mg Zeniquin® (marbofloxacin) tablet are bioequivalent in dogs.

B. Blood-level Bioequivalence Study in Cats

Title: Blood-level Bioequivalence Study in Cats: A masked, Balanced, Randomized, Two Period, Two Sequence, Single Oral Dose, Cross Over Bioequivalence Study of Marbofloxacin Tablet 25 mg and Zeniquin® (Marbofloxacin) Tablet 25 mg in Healthy Cats Under Fasting Conditions (Study No. 3118-0002).

Study Dates: March 3, 2021 to June 10, 2021

Study Locations:

In-life phase: Mattawan, Michigan

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 tablets and the RLNAD 50 mg Zeniquin® (marbofloxacin) tablets in fasted cats.

Study Animals: Eighteen male cats between the ages of 1 and 5 years and weighing 3.5-6.5 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 tablets 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 18 cats with a 9-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	37001.76†	39176.06†	0.94	0.88	1.01
C_{MAX} (ng/mL)	2666.57†	2895.26†	0.92	0.83	1.03
T_{MAX} (hours) (SD)‡	1.14 (1.14)‡	0.87 (0.84)‡	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 tablet and the RLNAD 25 mg Zeniquin® (marbofloxacin) tablet are bioequivalent in cats.

C. Bioequivalence Waiver

Two pivotal *in vivo* blood-level bioequivalence studies were conducted. One study was conducted using the 50 mg marbofloxacin tablet in dogs, and the other study was conducted using the 25 mg marbofloxacin tablet in cats. A biowaiver for the generic 25 mg, 100 mg, and 200 mg 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 25 mg, 50 mg, 100 mg, and 200 mg marbofloxacin tablets, as well as the RLNAD 25 mg and 50 mg marbofloxacin tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 50 mg and generic 25 mg tablets
- Generic 50 mg and generic 100 mg tablets
- Generic 50 mg and generic 200 mg tablets
- RLNAD 25 mg and generic 25 mg tablets
- RLNAD 25 mg and RLNAD 50 mg tablets

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

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.001 N HCl, pH = 3.0
- Dissolution medium volume: 900 mL
- Temperature: 37 ± 0.5°C
- Paddle speed: 75 rpm
- Number of vessels: 12
- Data points: 10, 15, 20, 30, 45, 60, and 90 minutes

The generic and RLNAD drug lot numbers used in the *in vivo* bioequivalence studies 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., 10 and 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 f_2 value 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
50 mg generic to the 25 mg generic	43.0
50 mg RLNAD to the 25 mg RLNAD	42.2
50 mg generic to the 100 mg generic	76.3
50 mg generic to the 200 mg generic	74.3
25 mg RLNAD to the 25 mg generic	57.0

Study results demonstrate similar dissolution profiles for two within-product comparisons (generic 50 mg tablet strength to generic 100 mg and 200 mg tablet strengths). The 50 mg generic tablet strength compared to the 25 mg generic tablet strength did not pass the $f_2 > 50$ criterion, and so the 50 mg RLNAD tablet strength was compared to the 25 mg RLNAD tablet strength. Since the 50 mg RLNAD tablet strength compared to the 25 mg RLNAD tablet strength also did not meet the $f_2 > 50$ criterion, the sponsor was able to compare the 25 mg generic tablet strength to the 25 mg RLNAD tablet strength, which met the $f_2 > 50$ criterion. Additionally, the *in vivo* study for cats demonstrated that the 25 mg tablets were equivalent *in vivo* for cats. Therefore, a biowaiver for the generic 25 mg, 100 mg, and 200 mg marbofloxacin 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:

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 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, when used

according to the label, is safe and effective for the indications listed in Section I.M. above.