

Date of Approval: March 23, 2020

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

ANADA 200-586

Marboquin™

(marbofloxacin)

Tablets

Dogs and Cats

Marboquin™ (marbofloxacin) tablets are indicated for the treatment of infections in dogs and cats associated with bacteria susceptible to marbofloxacin.

Sponsored by:

Dechra Veterinary Products LLC

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**I. GENERAL INFORMATION**

**A. File Number**

ANADA 200-586

**B. Sponsor**

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

Drug Labeler Code: 017033

**C. Proprietary Name**

Marboquin™

**D. Drug Product Established Name**

marbofloxacin

**E. Pharmacological Category**

Antibiotic

**F. Dosage Form**

Tablet

**G. Amount of Active Ingredient**

25 mg, 50 mg, 100 mg, and 200 mg

**H. How Supplied**

25 mg scored tablets supplied in bottles containing 100 tablets and 250 tablets

50 mg scored tablets supplied in bottles containing 100 tablets and 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**

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, Marboquin™ 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, Marboquin™ 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**

Marboquin™ (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 (RLNAD)**

Zeniquin®; marbofloxacin; NADA 141-151; 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, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD marbofloxacin tablet. One study was conducted using the 50 mg tablet in dogs, and one study was conducted using the 25 mg tablet in cats. The RLNAD is available in 25, 50, 100, and 200 mg tablet sizes. The *in vivo* blood-level study was conducted in 20 healthy, fasted dogs. Bioequivalence was demonstrated between the 50 mg Zeniquin® (marbofloxacin) Tablet and the 50 mg Marboquin™ (marbofloxacin) Tablet by demonstrating that the confidence limits for the difference between the pivotal parameters  $C_{MAX}$  and AUC are contained within the equivalence limits of 80.00% and 125.00%. There were no serious adverse events reported during the study. The *in vivo* blood-level study was conducted in 24 healthy, fasted cats. Bioequivalence was demonstrated between the 25 mg Zeniquin® (marbofloxacin) Tablet and the 25 mg Marboquin™ (marbofloxacin) Tablet by demonstrating that the confidence limits for the difference between the pivotal parameters  $C_{MAX}$  and AUC are contained within the equivalence limits of 80.00% and 125.00%. There were no serious adverse events reported during the study. 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. Dissolution data was used to demonstrate that the generic 25 mg, 50 mg, 100 mg, and 200 mg Marboquin™ (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 Marboquin™ (marbofloxacin) Tablets in dogs was granted. The study information is summarized below.

#### **A. Canine Blood-level Bioequivalence Study**

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of marbofloxacin tablets (50 mg).

1. Study Title:  
"A randomized, two sequence, two period crossover study to evaluate the bioequivalence of a test formulation of marbofloxacin (50 mg tablets) and a commercially available reference drug product (Zeniquin®, 50 mg tablets, Zoetis) in 20 fasted, healthy dogs"
2. Protocol:  
A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of marbofloxacin in 20 healthy, fasted dogs.
3. Testing Facilities:  
In-life phase: Carrentrila, Ballina,  
Co. Mayo, Ireland  
  
Bioanalytical testing: Fontenilles, France
4. Study Number:  
USA014\14-003
5. Objective:  
The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of Dechra Veterinary Products LLC's 50 mg marbofloxacin and the RLNAD 50 mg Zeniquin® (marbofloxacin) in a randomized, two-period, two-sequence, single-dose crossover study in dogs.
6. Measurement and Observation:  
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. No significant adverse events were recorded.
7. Statistical Methods:  
The laboratory study was conducted as a single-site, randomized, masked, two-period, two-sequence, two-treatment crossover design with a 7-day washout period between the two study periods, using 20 healthy dogs. Variables evaluated for bioequivalence are the maximum concentration ( $C_{max}$ ), time to maximum concentration ( $t_{max}$ ) and area under the concentration curve from time 0 to the last value above the limit of quantitation after  $C_{max}$  ( $AUC_{0-Last}$ ).  $C_{max}$  and  $t_{max}$  were determined from the observed concentrations.  $AUC_{0-Last}$  was calculated using a mixed log linear trapezoidal rule.

Due to dosing failures data collected from 1 dog in period 1 and 3 dogs in period 2 were discarded. A mixed effects model was used for the analysis, which included fixed effects of treatment, sequence and period, and random effects of the animal nested within sequence. Prior to analysis,  $AUC_{0-Last}$  and  $C_{max}$  were transformed onto the natural logarithmic scale. The two one-sided tests were performed to test bioequivalence, where the upper and lower bounds of the 90% confidence interval (CI) for the test to reference geometric mean ratio were calculated through the back transformation of the corresponding two bounds for the treatment difference in the logarithmic scale. Bioequivalence was concluded if the back-transformed upper and lower bounds for both geometric mean ratios of  $AUC_{0-last}$  and  $C_{max}$  were contained within the acceptance limits of 0.80 to 1.25. As seen in the table below, both  $AUC_{0-last}$  and  $C_{max}$  meet the bioequivalence criteria (Table II.1).

**Table II.1. Bioequivalence Evaluation of generic marbofloxacin and Zeniquin in dogs**

Variable	Test Mean*	Reference Mean*	Ratio†	Lower 90% CI	Upper 90% CI
$AUC_{0-Last}$ (ng/mL×hr)	38292	36784	1.04	1.01	1.08
$C_{max}$ (ng/mL)	3377	3233	1.06	1.00	1.12
$T_{max}$ (hr) (SD)	1.67 (0.73)	1.62 (0.73)			

Reference = Zeniquin (NADA 141-151); Test = Generic marbofloxacin

\* Geometric means for the test and reference except for  $T_{max}$  (arithmetic means and standard deviations (SD) are presented for  $T_{max}$ )

† Ratio = Test/Reference

## B. Feline Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of marbofloxacin tablets (25 mg).

- Study Title:  
"A randomized, two sequence, two period crossover study to evaluate the bioequivalence of a test formulation of marbofloxacin (25 mg tablets) and a commercially available reference drug product (Zeniquin®, 25 mg tablet, Zoetis) in 24 fasted, healthy cats"
- Protocol:  
A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of marbofloxacin tablets in 24 healthy, fasted cats.
- Testing Facilities:  
In-life phase: Carrentrila, Ballina,  
Co. Mayo, Ireland

Bioanalytical testing: Fontenilles, France

4. Study Number:  
USA014\14-002
5. Objective:  
The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence of Dechra Veterinary Products LLC's 25 mg marbofloxacin and the RLNAD 25 mg Zeniquin® (marbofloxacin) in a randomized, two-period, two-sequence, single-dose crossover study in cats.
6. Measurement and Observation:  
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. No significant adverse events were recorded.
7. Statistical Methods:  
The laboratory study was conducted as a single-site, randomized, masked, two-period, two-sequence, two-treatment crossover design with a 14-day washout period between the two study periods, using 24 healthy cats. The study was run in 2 sets for the purpose of study management. Each set contained 12 cats (6 cats were randomly selected from each sequence) and was dosed on the same day several hours apart. Variables evaluated for bioequivalence are the maximum concentration ( $C_{max}$ ), time to maximum concentration ( $t_{max}$ ) and area under the concentration curve from time 0 to the last value above the limit of quantitation after  $C_{max}$  ( $AUC_{0-Last}$ ).  $C_{max}$  and  $t_{max}$  were determined from the observed concentrations.  $AUC_{0-last}$  was calculated using a mixed log linear trapezoidal rule.

Due to dosing failures there were no plasma concentrations available for 2 cats in period 1 and 1 cat in period 2. No results were obtained for time 0 sample for 7 profiles. These values were set to missing prior to pharmacokinetic analyses. All values from 5 cats were excluded from statistical analysis due to an error in the calculation of dilution quality control concentration. A mixed effects model was used for the analysis, which included fixed effects of treatment, sequence and period, and random effects of the animal nested within sequence. Prior to analysis,  $AUC_{0-Last}$  and  $C_{max}$  were transformed onto the natural logarithmic scale. The two one-sided tests were performed to test bioequivalence, where the upper and lower bounds of the 90% confidence interval for the test to reference geometric mean ratio were calculated through the back transformation of the corresponding two bounds for the treatment difference in the logarithmic scale. Bioequivalence was concluded if the back-transformed upper and lower bounds for both geometric mean ratios of  $AUC_{0-last}$  and  $C_{max}$  were contained within the acceptance limits of 0.80 to 1.25. As seen in the table below, both  $AUC_{0-last}$  and  $C_{max}$  meet the bioequivalence criteria (Table II.2).

**Table II.2. Bioequivalence Evaluation of generic marbofloxacin and Zeniquin in cats**

Variable	Test Mean*	Reference Mean*	Ratio†	Lower 90% CI	Upper 90% CI
AUC <sub>0-Last</sub> (ng/mL×hr)	81874	76152	1.07	1.02	1.12
C <sub>max</sub> (ng/mL)	7165	6736	1.05	0.99	1.11
T <sub>max</sub> (hr) (SD)	0.97 (0.40)	1.09 (0.36)			

Reference = Zeniquin (NADA 141-151); Test = Generic marbofloxacin

\* Geometric means for the test and reference except for T<sub>max</sub> (arithmetic means and standard deviations (SD) are presented for T<sub>max</sub>)

† Ratio = Test/Reference

### C. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg marbofloxacin tablet strength in cats and the 50 mg marbofloxacin tablet strength in dogs. A waiver from the requirement to perform *in vivo* bioequivalence studies (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 Dechra Veterinary Products LLC's generic 25 mg, 100 mg, and 200 mg marbofloxacin tablets. The similarity factor (f<sub>2</sub>) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

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

The objective was to satisfy f<sub>2</sub> criteria between the RLNAD 25 mg, 50 mg, 100 mg and 200 mg tablet strengths and the corresponding generic dosage strengths: 25 mg, 50 mg, 100 mg, and 200 mg.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus 1, 10 mesh basket
- Dissolution medium: 0.1 N hydrochloric acid
- Dissolution medium volume: 900 mL
- Temperature: 37 ± 0.5 °C
- Paddle speed: 100 rpm
- Sampling Volume: 10 mL
- Data points: 15, 20, 30, 45, and 60 minutes (for 25 mg tablets); 15, 30, 45, and 60 minutes (for 50 mg, 100 mg, and 200 mg tablets)

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.3 below:

**Table II.3. Similarity ( $f_2$ ) Results**

Within- and between-product comparison

Between-product comparison

<b>Zeniquin®</b>	<b>Generic</b>	<b><math>f_2</math></b>
25 mg	25 mg	61
50 mg	50 mg	51
100 mg	100 mg	84
200 mg	200 mg	74

The study results demonstrate similar dissolution profiles for all the between-product comparisons, with  $f_2$  values > 50. Therefore, a biowaiver for the generic 25 mg, 100 mg, and 200 mg marbofloxacin tablet strengths 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 Marboquin™:

Not for human use. Consult a physician in cases of accidental ingestion by humans.

**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

This information submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that Marboquin™ when used according to the label, is safe and effective.