Date of Approval: March 11, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-720

Enroflox® Chewable Tablets

(enrofloxacin)

Dogs and Cats

Enroflox® Chewable Tablets (enrofloxacin) are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enroflox® Chewable Tablets are indicated for use in dogs and cats.

Sponsored by:

Norbrook Laboratories, Ltd.

Executive Summary

Enroflox® Chewable Tablets (enrofloxacin) are approved for the management of diseases associated with bacteria susceptible to enrofloxacin in dogs and cats. Enroflox® Chewable Tablets are a generic version of Baytril® Taste Tabs®.

	Proprietary Name	**Established Name**	**Application Type and Number**	**Sponsor**
Generic Animal Drug	Enroflox® Chewable Tablets	enrofloxacin	Abbreviated New Animal Drug Application (ANADA) 200-720	Norbrook Laboratories, Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	Baytril® Taste Tabs®	enrofloxacin	New Animal Drug Application (NADA) 140-441	Elanco US Inc.

Enrofloxacin, a fluoroquinolone antibiotic, has bactericidal activity against a broad spectrum of gram-negative and gram-positive bacteria. When given orally, enrofloxacin is rapidly absorbed from the digestive tract, penetrating into body tissues and 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 136 mg Enroflox® Chewable Tablets are bioequivalent to the 136 mg Baytril® Taste Tabs®. The sponsor also conducted one *in vivo* blood-level study in fasted cats to show that the 22.7 mg Enroflox® Chewable Tablets are bioequivalent to the 22.7 mg Baytril® Taste Tabs®. No serious adverse events were reported during either study.

Baytril® Taste Tabs® are available in 22.7, 68, and 136 mg tablets. To qualify for a waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for each of these product strengths in each species, a comparative *in vitro* dissolution study was conducted to determine the dissolution profiles of generic and RLNAD tablets of all strengths. All tablets showed rapid dissolution and/or similar comparative dissolution profiles. Therefore, the 22.7-mg and 68-mg strength Enroflox® Chewable Tablets qualified for a biowaiver in dogs and the 68-mg and 136-mg strength Enroflox® Chewable Tablets qualified for a biowaiver in cats. FDA

granted a biowaiver for the 22.7 mg and 68 mg tablet strengths in dogs and the 68 mg and 136 mg tablet strengths in cats.

User Safety
The labeling for Enroflox® Chewable Tablets includes a warning that people who have a history of hypersensitivity to quinolones 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 Enroflox® 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 200-720

B. Sponsor

Norbrook Laboratories, Ltd.
Carnbane Industrial Estate
Newry, County Down
BT35 6QQ UNITED KINGDOM

Drug Labeler Code: 055529

U.S. Agent Name and Address:
Melanie Archer
Norbrook, Inc.
9401 Indian Creek Parkway
Suite 680
Overland Park, KS 66210

C. Proprietary Name

Enroflox® Chewable Tablets

D. Drug Product Established Name

enrofloxacin

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

22.7 mg, 68 mg, or 136 mg of enrofloxacin per tablet

H. How Supplied

Each tablet strength is supplied in bottles containing 50 or 200 double scored tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Dogs: Administer orally at a rate to provide 5-20 mg/kg (2.27 to 9.07 mg/lb) of body weight. Selection of a dose within the range should be based on clinical experience, the severity of disease, and susceptibility of the pathogen. Animals

which receive doses in the upper-end of the dose range should be carefully monitored for clinical signs that may include inappetence, depression, and vomition.

Weight of Dog	**Once Daily Dosing Chart**			
	5.0 mg/kg	10.0 mg/kg	15.0 mg/kg	20.0 mg/kg
9.1 kg (20 lb)	2 X 22.7 mg tablets	1 X 22.7 mg plus 1 X 68 mg tablets	1 X 136 mg tablet	1 X 136 mg plus 2 X 22.7 mg tablets
27.2 kg (60 lb)	1 X 136 mg tablet	2 X 136 mg tablets	3 X 136 mg tablets	4 X 136 mg tablets

Cats: Administer orally at 5 mg/kg (2.27 mg/lb) of body weight.

Weight of Cat	**Once Daily Dosing Chart (5 mg/kg/day)**
5 lb (2.27 kg)	½ X 22.7 mg tablet
10 lb (4.5 kg)	1 X 22.7 mg tablet
15 lb (6.8 kg)	1 and ½ X 22.7 mg tablets or ½ X 68 mg tablet

The dose for dogs and cats may be administered either as a single daily dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. The dose should be continued for at least 2-3 days beyond cessation of clinical signs, to a maximum of 30 days.

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indications

Enroflox® Chewable Tablets (enrofloxacin) are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enroflox® Chewable Tablets are indicated for use in dogs and cats.

N. Reference Listed New Animal Drug (RLNAD)

Baytril® Taste Tabs®; enrofloxacin; NADA 140-441; Elanco US 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 enrofloxacin 136 mg chewable tablets in dogs and the 22.7 mg chewable tablets in cats. The RLNAD is available in 22.7, 68, and 136 mg chewable tablet sizes. The *in vivo* blood-level study in dogs was conducted in 24 healthy, fasted dogs and the *in vivo* blood-level study in cats was conducted in 20 healthy, fasted cats. 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 136 mg RLNAD and the 136 mg Enroflox® Chewable Tablets (enrofloxacin) in dogs and the 22.7 mg RLNAD and the 22.7 mg Enroflox® Chewable Tablets (enrofloxacin) in cats 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 22.7 mg and 68 mg chewable tablets in dogs, and for the generic 68 mg and 136 mg chewable tablets in cats was requested. Dissolution data was used to demonstrate that the generic 22.7 mg and 68 mg Enroflox® Chewable Tablets (enrofloxacin) are comparable to the generic 136 mg chewable tablet strength used in the *in vivo* blood-level bioequivalence dog study, and that the generic 68 mg and 136 mg Enroflox® Chewable Tablets (enrofloxacin) are comparable to the generic 22.7 mg chewable tablet strength used in the *in vivo* blood-level bioequivalence cat study. Therefore, a biowaiver for the generic 22.7 mg and 68 mg Enroflox® Chewable Tablets (enrofloxacin) in dogs and the 68 mg and 136 mg Enroflox® Chewable Tablets (enrofloxacin) in cats was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Dogs

Title: A Crossover Pharmacokinetic Study to Determine the Plasma Levels of Enrofloxacin in Dogs Following the Oral Administration of Enrofloxacin 136 mg Tablets (Norbrook Laboratories, Ltd., Product Code: T-ENRO-030) and Baytril® (enrofloxacin) Taste Tabs® 136 mg (Bayer HealthCare LLC., NADA 140-441). (Study No. 025/17)

Study Dates: September 19, 2017 to May 1, 2018

Study Locations:

In-life phase: Co. Down, Northern Ireland

Bioanalytical testing: Co. Down, Northern Ireland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 136 mg Enroflox® Chewable Tablets (enrofloxacin) and the RLNAD 136 mg Baytril® (enrofloxacin) Taste Tabs® in fasted dogs.

Study Animals: 24 beagle dogs (mix of female and male, neutered, and intact), 1 to 10 years of age, weighing between 11.1 to 14.7 kg.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study. The study was conducted according to the United Kingdom (UK) Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies, in accordance with GLP standards published as Organization for Economic Cooperation and Development (OECD) Principles of GLP.

Drug Administration: Each animal received 136 mg of either the generic or RLNAD enrofloxacin according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of enrofloxacin 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 beagle dogs with a 21-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 random effects of unit and subject nested within unit and 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 (ppm)*hour	2.1880†	2.1351†	1.7	0.93	1.20
C_{MAX} (ppm)	0.9558†	0.8688†	1.5	0.98	1.21
T_{MAX} (hours) (SD)‡	1.69 (0.55)‡	1.75 (0.72)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Test/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 136 mg Enroflox® Chewable Tablets (enrofloxacin) and the RLNAD are bioequivalent in dogs.

B. Blood-level Bioequivalence Study in Cats

Title: A Crossover Pharmacokinetic Study to Determine the Plasma Levels of Enrofloxacin in Cats Following the Oral Administration of Enrofloxacin Tablet 22.7mg (Norbrook Laboratories Ltd, T-ENRO-030) and Baytril® (enrofloxacin) Taste Tabs® 22.7 mg Antibacterial Tablets for Dogs and Cats (Bayer HealthCare LLC., NADA 140-441). (Study No. 024/17)

Study Dates: November 22, 2017 to August 8, 2018

Study Locations:

In-life phase: Co. Down, Northern Ireland

Bioanalytical testing: Co. Down, Northern Ireland

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 22.7 mg Enroflox® Chewable Tablets (enrofloxacin) and the RLNAD 22.7 mg Baytril® (enrofloxacin) Taste Tabs® in fasted cats.

Study Animals: 20 domestic shorthair cats (mix of female and male, neutered, and intact), 1 to 11 years of age, weighing between 4.4 to 6.02 kg.

Experimental Design: A randomized, masked, two-period, two-sequence, single-dose crossover study. The study was conducted according to the UK GLP for Nonclinical Laboratory Studies, in accordance with GLP standards published as OECD Principles of GLP.

Drug Administration: Each animal received 22.7 mg of either the generic or RLNAD enrofloxacin according to their randomized treatment sequence (generic/RLNAD or RLNAD/generic).

Measurements and Observations: The plasma concentrations of enrofloxacin 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 20 domestic shorthair cats with a 35-day washout between periods. Treatment administration was staggered over 5 days, with 2 cats from each sequence dosed each day. 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 random effects of set and subject nested within set and 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 (ppm)*hour	18.20†	18.75†	0.98	0.90	1.06
C_{MAX} (ppm)	2.16†	2.15†	1.01	0.92	1.13
T_{MAX} (hours) (SD)‡	1.10 (0.51)‡	0.96 (0.39)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = ratio geometric means (Test/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 22.7 mg Enroflox® Chewable Tablets (enrofloxacin) and the RLNAD are bioequivalent in cats.

C. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the generic 136 mg enrofloxacin chewable tablet strength in dogs and the generic 22.7 mg enrofloxacin chewable tablet strength in cats. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 22.7 mg and 68 mg chewable tablets in dogs, and for the generic 68 mg and 136 mg chewable tablets in cats was requested. To qualify for a biowaiver for each of these product strengths, a comparative *in vitro* dissolution study was conducted to determine the dissolution profiles of the generic and RLNAD 22.7 mg, 68 mg, and 136 mg enrofloxacin chewable tablets. When applicable, the similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 22.7 mg and generic 68 mg tablets
- Generic 22.7 mg and generic 136 mg tablets
- Generic 68 mg and generic 136 mg tablets
- Generic 22.7 mg and RLNAD 22.7 mg tablets
- Generic 68 mg and RLNAD 68 mg tablets
- Generic 136 mg and RLNAD 136 mg tablets

The objective was to satisfy f_2 criteria between the generic 136 mg chewable tablet strength and the generic and/or RLNAD 22.7 mg and 68 mg chewable tablet strengths and to satisfy f_2 criteria between the generic 22.7 mg chewable tablet strength and the generic and/or RLNAD 68 mg and 136 mg chewable tablet strengths.

Test conditions were as follows:
- Dissolution apparatus: USP Apparatus II
- Dissolution medium: 0.2% Citrate buffer, pH 4.0
- Dissolution medium volume: 900 ± 9 mL
- Temperature: 37 ± 0.5 °C
- Paddle speed: 100 rpm
- Number of vessels: 12
- Data points: 5, 10, 15, 20, 30 and 45 minutes

The generic and RLNAD lot numbers used in the *in vivo* bioequivalence studies (136 mg for dogs and 22.7 mg for 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 both products. The 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

Dissolution Comparison	Similarity Results
22.7 mg generic to the 68 mg generic	> 85% dissolved within 15 minutes supports sameness, f_2 not required.
22.7 mg generic to the 136 mg generic	37.7
68 mg generic to the 136 mg generic	59
22.7 mg generic to the 22.7 mg RLNAD	> 85% dissolved within 15 minutes supports sameness, f_2 not required.
68 mg generic to the 68 mg RLNAD	> 85% dissolved within 15 minutes supports sameness, f_2 not required.
136 mg generic to the 136 mg RLNAD	75.8

Study results demonstrate similar dissolution profiles for all comparisons, except the 22.7 mg generic did not satisfy the f_2 criterion of > 50 in comparison to the 136 mg generic tablet. The comparative dissolution strategy of generic strength to generic strength was not appropriate to show the equivalence between the generic 22.7 mg and the generic 136 mg tablets due to the rapid dissolution of the 22.7 mg tablet strength. Comparison of the 136 mg generic tablet to 136 mg RLNAD tablet met the f_2 criterion, satisfying the requirements to grant a biowaiver for that strength. When comparative profiles between tablets do not require an f_2 test because of rapid dissolution or when the f_2 value is ≥ 50, the product strengths used in the comparison qualify for a biowaiver. Therefore, a biowaiver for the generic 22.7 mg and 68 mg enrofloxacin chewable tablets in dogs, and the generic 68 mg and 136 mg enrofloxacin chewable tablets in cats 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 Enroflox® 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 quinolones 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 Enroflox® Chewable Tablets, when used according to the label, is safe and effective for the indications listed in Section I.M. above.