Date of Approval:April 19, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-551

Enrofloxacin Flavored Tablets

(enrofloxacin)

Tablets

Cats and dogs

For the management of diseases associated with bacteria susceptible to enrofloxacin.

Sponsored by:

Putney, Inc.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-551

B. Sponsor

Putney, Inc.
400 Congress St., suite 200
Portland, ME 04101

Drug Labeler Code: 026637

C. Proprietary Name

Enrofloxacin Flavored Tablets

D. Established Name

enrofloxacin

E. Pharmacological Category

Antibacterial

F. Dosage Form

Oral tablet

G. Amount of Active Ingredient

22.7 mg, 68 mg, and 136 mg

H. How Supplied

Bottles containing 22.7 mg: 100 & 500 count
Bottles containing 68 mg: 50 & 200 count
Bottles containing 136 mg: 50 & 200 count

I. Dispensing Status

Rx

J. Dosage Regimen

Cats: administer orally at 5 mg/kg (2.27 mg/lb) of body weight. The dose for dogs and cats may be administered either as a single daily dose or divided into two equal daily doses administered at twelve hour intervals.

Dogs: administer orally at a rate to provide 5-20 mg/kg (2.27-9.07 mg/lb) of body weight. Selection of 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 inappetance, depression, and vomition.

K. Route of Administration

Oral

L. Species/Class

Cats and dogs

M. Indication

For the management of diseases associated with bacteria susceptible to enrofloxacin.

N. Reference Listed New Animal Drug

BAYTRIL TASTE TABS; (enrofloxacin); NADA 140-441; Bayer Healthcare LLC, Animal Health Division

II. BIOEQUIVALENCE:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug or RLNAD). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA. Information to show that the generic version is bioequivalent to the approved RLNAD is required for approval.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence, using the generic and RLNAD enrofloxacin 22.7 mg in cats and 136 mg tablets in dogs. Additionally, *in vitro* dissolution studies comparing the generic and RLNAD products were conducted to meet the criteria for a waiver of the requirements to demonstrate *in vivo* bioequivalence for the 68 mg and 136 mg tablets in cats and for the 22.7 mg and 68 mg tablets in dogs for generic enrofloxacin tablets.

A. Blood-level Bioequivalence Studies

CATS:
One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of enrofloxacin (22.7 mg) tablets.

1. Protocol:
   A randomized, two-way crossover, single dose, replicate design bioequivalence study to evaluate the relative bioavailability of a generic tablet formulation of enrofloxacin (22.7 mg) compared to an equivalent dose of a commercially available reference drug product BAYTRIL TASTE TABS (enrofloxacin) (22.7 mg, Bayer Healthcare LLC, Animal Health Division) was performed in 20, fasted, healthy mixed breed cats.

2. Testing Facility:
   Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

3. Study Number:
   USA014\10-001

4. Objective:
   The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of Putney, Inc.'s 22.7 mg generic enrofloxacin tablets and Bayer's 22.7 mg BAYTRIL TASTE TABS (enrofloxacin), in a two-way crossover, single dose, study in cats.

5. Study Summary:
   The study was conducted as a 2-period, 2-treatment crossover design using 20 cats with a 14 day washout between periods. The study was conducted in 2 sets one day apart, where each time set is balanced for sequence group. Variables evaluated are area under the concentration (AUC) curve from time 0 to the first value below the limit of quantitation and the observed maximum concentration (CMAX) and time to maximum concentration (TMAX). The statistical model included sequence, treatment, and period as fixed effects, and set and animal-within-sequence-by-set as random effects.

   The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus RLNAD, based on the natural log scale of AUC and CMAX and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00%. As seen in the table below both AUC and CMAX fall within the prescribed bounds. TMAX values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

   Table 1 Bioequivalence Evaluation

Variable	Generic Mean	RLNAD Mean	Lower Bound	Upper Bound
AUC (ng/mL)*hour	22518*	21575*	100.2%	110.2%
CMAX (ng/mL)	2562*	2345*	100.9%	119.5%
TMAX (hour)	0.84†	0.88†	NA	NA

*Geometric Mean
†Arithmetic Mean

DOGS:
One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of enrofloxacin (136 mg) tablets.

1. Protocol:
   A randomized, two-way crossover, single dose, replicate design bioequivalence study to evaluate the relative bioavailability of a generic tablet formulation of enrofloxacin (136 mg) compared to an equivalent dose of a commercially available reference drug product BAYTRIL TASTE TABS (enrofloxacin) (136 mg, Bayer Healthcare LLC, Animal Health Division) was performed in 20, fasted, healthy beagle dogs.

2. Testing Facility:
   Charles River Laboratories Preclinical Services Ireland Ltd., Glenamoy, Ballina, Co. Mayo, Ireland

3. Study Number:
   USA014\10-002

4. Objective:
   The objective of this study was to determine the comparative *in vivo* blood level bioequivalence of Putney, Inc.'s 136 mg generic enrofloxacin tablets and Bayer's 136 mg BAYTRIL TASTE TABS (enrofloxacin), in a two-way crossover, single dose study in dogs.

5. Study Summary:
   The study was conducted as a 2-period, 2-treatment crossover design using 20 dogs with a 7 day washout between periods. Dogs were ranked from heaviest to lightest based on Day -1 body weight. Dogs were randomized to sequence group within sequential pairs (weight blocks) using random order numbers. Variables evaluated are area under the concentration (AUC) curve from time 0 to the first value below the limit of quantitation and the observed maximum concentration (CMAX) and time to maximum concentration (TMAX). The statistical model included sequence, treatment, and period as fixed effects, and replicate (weight blocks based on Day -1 body weight) and sequence-by-replicate interaction as random effects.

   The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus RLNAD, based on the natural log scale of AUC and CMAX and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00%. As seen in the table below both AUC and CMAX fall within the prescribed bounds. TMAX values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

   Table 2 Bioequivalence Evaluation

Variable	Generic Mean	RLNAD Mean	Lower Bound	Upper Bound
AUC (ng/mL)*hour	10963*	10931*	98.9%	103.8%
CMAX (ng/mL)	2811*	2785*	94.5%	107.4%
TMAX (hour)	1.76†	1.80†	NA	NA

*Geometric Mean
†Arithmetic Mean

B. Bioequivalence Waiver

Pivotal *in vivo* blood level bioequivalence studies were conducted using the 22.7 mg enrofloxacin chewable tablet strength in cats, and the 136 mg enrofloxacin chewable tablet strength in dogs.

A waiver of the requirement to demonstrate bioequivalence (biowaiver) for the generic 22.7 mg and 68 mg enrofloxacin chewable tablets for dogs, and the 68 mg and 136 mg chewable tablets for cats was requested. To qualify for a biowaiver for each of these product strengths, comparative dissolution studies were conducted to determine the dissolution profiles of the respective generic and RLNAD 22.7 mg, 68 mg, and 136 mg enrofloxacin chewable tablets in citrate buffer at a pH of 4.0. The similarity factor (f2) calculation was used to evaluate dissolution profile comparisons. The dissolution studies compared the following 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.

Dissolution parameters:

Apparatus:	USP/EP apparatus I
Medium:	Citric acid/NaOH/H_2O/HCl pH adjusted
Volume:	900 mL vacuum degassed medium
RPM:	100
Temperature:	37°C ± 0.5°C
Evaluation sets:	12 dosage units of test and reference products
Analysis:	UV spectrophotometer (λ= 278 nm)
Sampling times:	10, 15, 30, and 45 minutes
Profile comparison:	Similarity factor (f2)

The selection of the apparatus type, *in vitro* testing conditions, and sampling times was based on developing a discriminatory method that could detect significant differences between the dissolution profile of the test and reference products. The biolots used in the *in vivo* bioequivalence study (22.7 mg for cats and 68 mg in dogs) were the same lots of products for both the generic and reference products 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.

Table 3 Results for Dissolution Studies

Dissolution Comparison	f2 (≥ 50 indicates sameness)
22.7 mg generic to the 22.7 mg RLNAD	> 85% dissolution in 15 minutes. No f2 required
68.0 mg generic to the 68.0 mg RLNAD	> 85% dissolution in 15 minutes. No f2 required
136 mg generic to the 136 mg RLNAD	f2 = 63*

*Mean value of 12 dissolution tests

In comparing dissolution profiles f2 values ≥50 indicate sameness. The study design requires that no more than 2 data points beyond > 85% dissolution be included in the calculation of the f2 metric. Additionally, the percent coefficient of variation for all generic product profiles should fall within the acceptable limits of less than 10%. In cases where both the generic and RLNAD tablets are > 85% dissolved in less than 15 minutes, a dissolution profile comparison using the f2 test is unnecessary. When comparative profiles between the test and reference products do not require an f2 test because of rapid dissolution or when the f2 value is ≥50, the product strength used in the comparison qualifies for a biowaiver.

Study results demonstrate similar dissolution profiles for the generic and RLNAD 22.7 mg, 68 mg, and 136 mg enrofloxacin chewable tablets. The percent coefficient of variation for all generic product profiles was less than 10% (data not shown). Therefore, a waiver of the requirement to demonstrate *in vivo* bioequivalence for the generic 22.7 mg and 68 mg enrofloxacin chewable tablets in dogs, and the 68 mg and 136 mg generic enrofloxacin chewable tablets in cats was granted.

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY:

Data on human food safety, pertaining to drug residues in food, were not required for approval of this application. This drug is approved for use in cats and dogs, which are not food producing animals.

VI. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Enrofloxacin Flavored Tablets:

- For use in animals only.
- Keep out of reach of children.

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that Enrofloxacin Flavored Tablets, when used according to the label, are safe and effective.