Date of Approval: July 30, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-608

Baytril® Soft Chewable Tablets

(enrofloxacin)

Dogs and cats

For the management of diseases associated with bacteria susceptible to enrofloxacin

Sponsored by:

Piedmont Animal Health

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-608

B. Sponsor

Piedmont Animal Health
204 Muirs Chapel Rd.
Suite 200
Greensboro, NC 27410

Drug Labeler Code: 086088

C. Proprietary Name

Baytril® Soft Chewable Tablets

D. Product Established Name

enrofloxacin

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Chewable Tablet

G. Amount of Active Ingredient

22.7, 68.0, or 136.0 milligrams (mg) enrofloxacin

H. How Supplied

22.7 mg X 60 count bottle
68.0 mg X 60 count bottle
136.0 mg X 60 count bottle

I. Dispensing Status

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.

Table I.1. Once Daily Dosing Chart for dogs

Weight of Dog	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

All tablet sizes are double scored for accurate dosing.

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 (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.

Table I.2. Once Daily Dosing Chart for cats

Weight of Cat	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

All tablet sizes are double scored for accurate dosing.

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indication

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

N. Reference Listed New Animal Drug

Baytril® Taste Tabs® Antibacterial Tablets; 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 (GADPTRA) 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 (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.

The sponsor submitted a suitability petition (FDA-2012-P-0497-0001/CP) requesting permission to submit an ANADA for a generic new animal drug that differed in change in dosage form from the RLNAD. This was a request for a change from a compressed

(hard) tablet to a soft chewable tablet. This petition was approved on August 31, 2012, under 512(n)(3)(C) of the Federal Food, Drug, and Cosmetic Act.

For this ANADA, two *in vivo* blood-level studies were conducted, to demonstrate product bioequivalence, using the generic and reference listed new animal drug (RLNAD) enrofloxacin 22.7 mg in cats and 136 mg tablets in dogs. No significant adverse effects were seen in either study. The RLNAD is available as 22.7 mg, 68 mg, and 136 mg tablets. Additionally, *in vitro* comparative dissolution studies were conducted to meet the criteria for a waiver from the requirement to perform *in vivo* bioequivalence studies for the 68 mg and 136 mg generic enrofloxacin tablets in cats, and the 22.7 mg, and 68 mg tablets in dogs.

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, 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® (enrofloxacin) Taste Tabs® Antibacterial Tablets (22.7 mg, Bayer Healthcare LLC, Animal Health Division) was performed in 24 purpose-bred neutered male and intact female cats.

2. Testing Facility:
   Kingfisher International Inc., ON, Canada

3. Study Number:
   KFI-062-BF-2813 (Sponsor Study No.: P13-017)

4. Objective:
   To determine the comparative *in vivo* blood level bioequivalence of Piedmont's generic enrofloxacin soft chewable tablets vs. Baytril® (enrofloxacin) Taste Tabs® in cats.

5. Study Summary:
   The study was conducted as a single dose, randomized, two-sequence, cross-over design using 24 cats with a 14-day washout between periods. A mixed effects model was used to analyze data. The statistical model included sequence, period, and treatment as the fixed effects, and the subject within the sequence as a random effect. Period was modeled as a repeated factor with group=treatment and subject=subject as options in the repeated statement.

   Variables evaluated were area under the curve (AUC) from time 0 to the time of the last quantifiable concentration and the observed maximum concentration (C_{MAX}). For both AUC_{tlast} and C_{max}, the upper and lower confidence limits of the transformed data were back-transformed to estimate the upper and lower bounds of the ratio of test to reference product. The criteria for determining

bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the natural log scale of AUC and C_{max} 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 (Table II.1) both AUC and C_{max} fall within the prescribed bounds. T_{max} values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

Table II.1. Bioequivalence Evaluation

Parameter	Test Mean	Reference Mean	Ratio of Geometric Means (T/R)	Lower Bound (%)	Upper Bound (%)
AUC_{tlast} (hr*ng/mL)	22514.2	24245.8	92.9	88.6	97.3
C_{max} (ng/mL)	1724.2†	2039.2†	84.6	81.4	87.8
T_{max} (hour)	1.71‡	0.96‡	N/A	N/A	N/A

† 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, 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® (enrofloxacin) Taste Tabs® Antibacterial Tablets (136 mg, Bayer Healthcare LLC, Animal Health Division) was performed in twenty-four (24) purpose-bred male beagle dogs.

2. Testing Facility:
   Kingfisher International Inc., ON, Canada

3. Study Number:
   KFI-062-BC-1715 (Sponsor Study No: P15-026)

4. Objective:
   To determine the comparative *in vivo* blood level bioequivalence of Piedmont's generic enrofloxacin soft chewable tablets vs. Baytril® (enrofloxacin) Taste Tabs® in healthy, fasted dogs.

5. Study Summary:
   The study was conducted as a single dose, randomized, two-sequence, cross-over design using 24 dogs with a 14-day washout between periods. All statistical analyses were based on the proposed study design with the individual animal as the experimental unit. The analyses were done on the log-transformed data using the linear mixed model with sequence, period, and

product as fixed effects. Subject within sequence was included as a random effect.

Variables evaluated are area under the curve (AUC) from time 0 to the time of the last quantifiable concentration and the observed maximum concentration (C_{MAX}). AUC_{tlast} and C_{max} values were Ln-transformed prior to the analysis. The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the natural log scale of AUC and C_{max} 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 (Table II.2) both AUC and C_{max} fall within the prescribed bounds. T_{max} values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

Table II.2. Bioequivalence Evaluation

Parameter	Test Mean	Reference Mean	Ratio of Geometric Means (T/R)	Lower Bound (%)	Upper Bound (%)
AUC_{tlast} (hr*ng/mL)	15011.54†	15597.50†	0.96	0.91	1.02
C_{max} (ng/mL)	2714.0†	2789.0†	0.97	0.93	1.01
T_{max} (hour)	1.7‡	1.7‡	N/A	N/A	N/A

†Geometric mean
‡Arithmetic mean

B. Bioequivalence Waiver

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

A waiver from the requirement to perform *in vivo* bioequivalence (biowaiver) studies for the generic 68 mg and 136 mg soft chewable tablets in cats and the 22.7 mg and 68 mg soft chewable tablets in dogs 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 generic 22.7 mg, 68 mg, and 136 mg tablets versus the tablet strengths used in the *in vivo* studies. The similarity factor (f_2) calculation is used to evaluate the similarity of the dissolution profiles. The following dissolution profile comparisons for the generic product strengths were evaluated:

- 22.7 mg and 136 mg tablets
- 22.7 mg and 68 mg tablets
- 136 mg and 68 mg tablets

Dissolution Parameters:

- Apparatus: USP Apparatus 2 (paddles)
- Temperature: 37.0 °C ± 0.5 °C
- Rotation Speed: 100 rpm
- Sampling Point(s):
    - Standard: 60 minutes

  - Profile: 5, 10, 15, 30, 45, 60, and 90 minutes
- Number of Tablets to Analyze:
  - Standard: 6 per current USP <171>
  - Profile: n=12
- Dissolution Medium: 50 mM citrate buffer, pH = 4.0
- Dissolution Medium: 1000 mL
- Specification: NLT 75% (Q) of enrofloxacin is dissolved in 90 minutes

The selection of the apparatus type, *in vitro* testing conditions, and sampling times were based on developing a discriminatory method that could detect significant differences between the dissolution profile of the test and reference products (Table II.3). The biolots used in the *in vivo* bioequivalence study were the same lots of reference and generic products used to support the *in vitro* profile comparisons. Analytical method validation was required to ensure that the quantification of drug concentration in all samples was accurate and precise.

In comparing dissolution profiles, f_2 values greater than or equal to 50 indicate sameness. The study design requires that no more than 1 data point beyond 85% dissolution be included in the calculation of the f_2 metric. Additionally, to allow use of mean data in the calculation of f_2, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 minutes), and should not be more than 10% at other time points.

Table II.3. Dissolution Profiles for Generic Product Strengths*

Generic Product Strength	5 min	10 min	15 min	30 min	45 min	60 min	90 min
22.7 mg	28.83	49.93	65.89	89.90	97.38	97.99	97.67
68 mg	22.64	40.78	55.40	80.72	90.33	93.90	94.34
136 mg	25.69	46.80	63.77	91.29	97.34	98.82	99.28

* Data shown are the mean of percent released (n=12)

The lot numbers of the 22.7 mg and 136 mg generic tablet strengths are the same as those used in the *in vivo* bioequivalence studies. Dissolution profiles of all other generic tablet strengths were compared to the profile of those two lots (Table II.3). The calculated f_2 values between each profile are as follows:

Table II.4. Calculated f_2 values

Tablet strength	22.7 mg	68 mg
68 mg	52.4	N/A
136 mg	78.1	56.0

The study results demonstrate similar dissolution profiles for all strengths of the generic product.

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 dogs and cats, which are not food producing animals.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Baytril® Soft 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.

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 Baytril® Soft Chewable Tablets, when used according to the label, are safe and effective.