Date of Approval: June 20, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-517

ZOBUXA

enrofloxacin

Flavored Antibacterial Tablets

Cats and dogs

For the management of diseases associated with bacteria susceptible to enrofloxacin

Sponsored by:

Novartis Animal Health US, Inc.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-517

B. Sponsor

Novartis Animal Health US, Inc.
3200 Northline Ave., suite 300
Greensboro, NC 27408

Drug Labeler Code: 058198

C. Proprietary Name

ZOBUXA

D. Established Name

enrofloxacin

E. Pharmacological Category

Antibacterial

F. Dosage Form

Flavored Antibacterial Tablet

G. Amount of Active Ingredient

22.7 mg, 68 mg, 136 mg, and 272 mg

H. How Supplied

Bottles containing 22.7 mg tablets: 100 and 500 counts
Bottles containing 68 mg tablets: 50 and 150 counts
Bottles containing 136 mg tablets: 50 count
Bottles containing 272 mg tablets: 50 count

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.

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 doses 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

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). 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.

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. The RLNAD is available as 22.7 mg, 68 mg, and 136 mg tablets. A suitability petition (FDA-2009-P-0245-0001/CP) was granted for the addition of a 272 mg tablet for the generic product. Additionally, *in vitro* comparative dissolution studies were conducted to meet the criteria for a waiver of the requirements to demonstrate bioequivalence for the 68 mg and 136 mg generic enrofloxacin tablets in cats, and the 22.7 mg, 68 mg, and 272 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 TASTE TABS (enrofloxacin) (22.7 mg, Bayer Healthcare LLC, Animal Health Division) was performed in 16, fasted, healthy, male European Short Haired cats.

2. Testing Facility:
   Avogadro, Parc de Génibrat, 31470 Fontenilles, France

3. Study Number:
   A092668

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

5. Study Summary:
   The study was conducted as a two-period, two-treatment crossover design using 15 cats with a 14 day washout between periods. 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). The statistical model included sequence, treatment, and period as fixed effects, and animal-within-sequence as a random effect.

   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 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 (Table 1) 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	19961*	18461*	99.9%	117.1%
CMAX (ng/mL)	2021*	1914*	98.9%	112.7%
TMAX (hour)	1.40†	1.37†	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 TASTE TABS (enrofloxacin) (136 mg, Bayer Healthcare LLC, Animal Health Division) was performed in 16, fasted, healthy, male Beagle dogs.

2. Testing Facility:
   Avogadro, Parc de Génibrat, 31470 Fontenilles, France

3. Study Number:
   A092667

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

5. Study Summary:
   The study was conducted as a two-period, two-treatment crossover design using 16 dogs with a 7 day washout between periods. 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). The statistical model included sequence, treatment, and period as fixed effects, and animal-within-sequence as a random effect.

   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 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 (Table 2) 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	14012*	13592*	99.0%	107.4%
CMAX (ng/mL)	4346*	4296*	94.4%	108.5%
TMAX (hour)	1.10†	1.38†	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 flavored tablet strength in cats, and the 136 mg enrofloxacin flavored tablet strength in dogs.

A waiver of the requirement to demonstrate bioequivalence (biowaiver) for the generic 68 mg and 136 mg flavored tablets in cats, and the 22.7 mg, 68 mg, and 272 mg flavored 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 RLNAD 22.7 mg and 136 mg tablets, as well as the generic 22.7 mg, 68 mg, 136 mg, and 272 mg tablets. The similarity factor (f_2) calculation is used to evaluate dissolution profiles where both tablets are ≤ 85% dissolved in less than 15 minutes. 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
- 22.7 mg and 272 mg tablets
- 136 mg and 68 mg tablets
- 136 mg and 272 mg tablets

Dissolution parameters:

Dissolution media:	0.01 M hydrochloric acid + 0.05 M sodium chloride, pH 2.0 0.05 M sodium acetate buffer, pH 4.5 0.05 M potassium dihydrogen phosphate buffer, pH 6.8
Volume:	1000 mL
Apparatus:	Paddle
Paddle speed:	75 rpm
Temperature:	37°C ± 0.5°C
Detection:	UV 277 nm (22.7 mg, 68 mg, 136 mg) UV 316 nm (272 mg)
Sampling time:	5, 10, 15, 30, and 45 min

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 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 ≥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. In cases where both the tablets are > 85% dissolved in less than 15 minutes, a dissolution profile comparison using the f_2 test is unnecessary. When comparative profiles between tablets do not require an f_2 test because of rapid dissolution or when the f_2 is ≥50, the product strength used in the comparison qualifies for a biowaiver.

Table 3. Dissolution Profiles for Generic Product Strengths*

Generic Product Strength	5 min	10 min	15 min	30 min	45 min
22.7 mg	50	97	100	101	101
68 mg	31	68	97	100	100
136 mg	39	79	98	99	99
272 mg	32	64	89	99	100

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

The lot numbers of 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 (see Table 4).

Study results demonstrate similar dissolution profiles for all strengths of the generic product. The percent coefficient of variation for all product profiles was less than 10% (data not shown). Because all products released greater than 85% within 15 minutes, the dissolution profiles are deemed similar without estimation of f_2 factors.

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:

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 ZOBUXA:

- 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 ZOBUXA, when used according to the label, is safe and effective.