Date of Approval: September 8, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-592

Amoxicillin Trihydrate and Clavulanate Potassium Tablets

amoxicillin trihydrate and clavulanate potassium

Dogs and cats

Amoxicillin Trihydrate and Clavulanate Potassium Tablets are indicated in the treatment of:

Dogs: Skin and soft tissue infections such as wounds, abscesses, cellulitis, superficial/juvenile and deep pyoderma due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., and *E. coli*. Periodontal infections due to susceptible strains of both aerobic and anaerobic bacteria. Amoxicillin trihydrate and clavulanate potassium tablets have been shown to be clinically effective for treating cases of canine periodontal disease.

Cats: Skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., *E. coli*, and *Pasteurella* spp. Urinary tract infections (cystitis) due to susceptible strains of *E. coli*.

Sponsored by:

Putney, Inc.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-592

B. Sponsor

Putney, Inc.
One Monument Sq.
Suite 400
Portland, ME 04101

Drug Labeler Code: 026637

C. Proprietary Name

Amoxicillin Trihydrate and Clavulanate Potassium Tablets

D. Product Established Name

Amoxicillin trihydrate and clavulanate potassium

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Tablet

G. Amount of Active Ingredient

62.5 mg (50 mg amoxicillin, 12.5 mg clavulanic acid)
125 mg (100 mg amoxicillin, 25 mg clavulanic acid)
250 mg (200 mg amoxicillin, 50 mg clavulanic acid)
375 mg (300 mg amoxicillin, 75 mg clavulanic acid)

H. How Supplied

Each carton holds 15 strips with 14 tablets per strip (210 tablets per carton)

I. Dispensing Status

Rx

J. Dosage Regimen

Dogs: The recommended dosage is 6.25 mg/lb of body weight twice a day.

Skin and soft tissue infections such as abscesses, cellulitis, wounds, superficial/juvenile pyoderma, and periodontal infections should be treated for 5-7 days or for 48 hours after all symptoms have subsided. If no response is seen after 5 days of treatment, therapy should be discontinued and the case

reevaluated. Deep pyoderma may require treatment for 21 days; the maximum duration of treatment should not exceed 30 days.

Cats: The recommended dosage is 62.5 mg twice a day.

Skin and soft tissue infections such as abscesses and cellulitis/dermatitis should be treated for 5-7 days or for 48 hours after all symptoms have subsided, not to exceed 30 days. If no response is seen after 3 days of treatment, therapy should be discontinued and the case reevaluated.

Urinary tract infections may require treatment for 10-14 days or longer. The maximum duration of treatment should not exceed 30 days.

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indications

Amoxicillin Trihydrate and Clavulanate Potassium Tablets are indicated in the treatment of:

Dogs: Skin and soft tissue infections such as wounds, abscesses, cellulitis, superficial/juvenile and deep pyoderma due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., and *E. coli*. Periodontal infections due to susceptible strains of both aerobic and anaerobic bacteria. Amoxicillin trihydrate and clavulanate potassium tablets have been shown to be clinically effective for treating cases of canine periodontal disease.

Cats: Skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., *E. coli*, and *Pasteurella* spp. Urinary tract infections (cystitis) due to susceptible strains of *E. coli*.

N. Reference Listed New Animal Drug

CLAVAMOX; amoxicillin trihydrate and clavulanate potassium; NADA 055-099; Zoetis Inc.

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 RLNAD is available in four strengths of 62.5 mg, 125 mg, 250 mg, and 375 mg compressed, film-coated tablets. Only the 62.5 mg tablet is labeled for use in cats. For this ANADA, the sponsor conducted two pivotal blood level bioequivalence studies; one in cats using the 62.5 mg tablets, another in dogs using the 125 mg tablets. Additionally, *in vitro* comparative dissolution studies were conducted to meet the criteria for a waiver from the requirement to demonstrate bioequivalence (biowaiver) for the 62.5 mg, 250 mg, and 375 mg tablets in dogs.

A. Blood-level Bioequivalence Studies

DOGS:

One blood level bioequivalence study was conducted to evaluate the bioequivalence between the generic and RLNAD formulations of amoxicillin trihydrate and clavulanate potassium (125 mg) tablets.

1. Objectives:

   The purpose of the study was to evaluate the bioequivalence between the generic amoxicillin trihydrate and clavulanate potassium tablets (125 mg) and the commercially available CLAVAMOX (amoxicillin trihydrate and clavulanate potassium) tablets (125 mg) in a randomized, two-sequence, four-period replicate-designed, crossover study performed in forty healthy, intact male beagle dogs at fasted condition.

2. Testing Facilities:

   a. In-life test facility
      Auxvasse
      Missouri, USA

   b. Bioanalytical test facility
      Nürnberg-Heroldsberg, Germany

3. Study Title:

   Pivotal Bioequivalence Study of Putney's Generic Amoxicillin/Clavulanic Acid Tablets (125 mg) vs. Clavamox Tablets (125 mg) in Beagle Dogs (S12865)

4. Results:

   The study was conducted as a two-sequence, four-period, crossover design using 40 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 (C_{MAX}).

   For the analysis of amoxicillin, the statistical model included sequence, treatment, and period as fixed effects, and animal-within-sequence and animal-within-room as random effects. 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%.

For the analysis of clavulanic acid, the reference-scaled average bioequivalence approach including all 4 treatment periods was used to evaluate the bioequivalence for both AUC and C_{MAX} because the within subject standard deviation for the reference article (S_{WR}) of the log-transformed data for both AUC and C_{MAX} was ≥0.294. To declare bioequivalence, the point estimate of the test/reference geometric mean ratio needed to fall within 0.8 and 1.25, and the upper 95% confidence bound for the difference in log-transformed AUC tlast and/or C_{MAX} needed to be ≤0. The 95% upper bound was calculated as follows:

$$(\text{test product ln-transformed mean} - \text{control product ln-transformed mean})^2 - \Theta(S_{WR})^2$$

where Θ was defined as $((\ln(1.25)/\sigma_{W0}))^2$, and $\sigma_{W0} = 0.25$.

As seen in the table below both AUC and C_{MAX} meet the bioequivalence criteria for both amoxicillin (Table 1) and clavulanic acid (Table 2). T_{MAX} values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

Table 1. Bioequivalence Evaluation of Amoxicillin in Dogs

Variable	Generic Mean	RLNAD Mean	Lower Bound	Upper Bound
AUC (µg/mL) *hour	18.26*	18.82*	88%	106%
C_{MAX} (µg/mL)	6.31*	6.51*	87%	107%
T_{MAX} (hour)	1.47†	1.48†	NA	NA

* Geometric Mean
† Arithmetic Mean

Table 2. Bioequivalence Evaluation of Clavulanic Acid in Dogs

Variable	Generic Mean	RLNAD Mean	Generic/ RLNAD Mean	95% Upper Bound
AUC (µg /mL) *hour	NA	NA	0.92*	-0.034
C_{MAX} (µg /mL)	NA	NA	0.92*	-0.037
T_{MAX} (hour)	1.01†	1.03†	NA	NA

* Geometric Mean
† Arithmetic Mean

5. Conclusion:

The generic amoxicillin trihydrate and clavulanate potassium 125 mg tablets are bioequivalent to CLAVAMOX 125 mg tablets in dogs.

CATS:

One blood level bioequivalence study was conducted to evaluate the bioequivalence between the generic and RLNAD formulations of amoxicillin trihydrate and clavulanate potassium (62.5 mg) tablets.

1. Objectives:

   The study was to evaluate the bioequivalence between the generic amoxicillin trihydrate and clavulanate potassium tablets (62.5 mg) and the commercially available CLAVAMOX (amoxicillin trihydrate and clavulanate potassium) tablets (62.5 mg) in a randomized, two-sequence, two-period, crossover study performed in thirty healthy, intact female European mixed breed cats at fasted condition.

2. Testing Facilities:

   a. In-life test facility
      Co. Mayo, Ireland

   b. Bioanalytical facility
      Nürnberg-Heroldsberg, Germany

3. Study Title:

   A Randomized, Two Sequence, Two Period Crossover Study to Evaluate the Bioequivalence of a Test Oral Tablet Formulation of Amoxicillin (50 mg) and Clavulanic Acid (12.5 mg) and a Commercially Available Reference Drug Product (Clavamox Tablets, Zoetis) in 30 Fasted Healthy Cats (USA014\14-005)

4. Results:
   The study was conducted as a two-sequence, two-period, crossover design using 30 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 (C_{MAX}). 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 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 AUC and C_{MAX} fall within the prescribed bounds for both amoxicillin (Table 3) and clavulanic acid (Table 4). T_{MAX} values obtained for the test and reference product indicate that these drugs will provide equivalent therapeutic results.

Table 3. Bioequivalence Evaluation of Amoxicillin in Cats

Variable	Generic Mean	RLNAD Mean	Lower Bound	Upper Bound
AUC (µg/mL) *hour	42.38*	42.42*	94.4%	106.6%
C_{MAX} (µg/mL)	10.15*	10.38*	91.8%	104.9%
T_{MAX} (hour)	2.36†	2.09†	NA	NA

* Geometric Mean
† Arithmetic Mean

Table 4. Bioequivalence Evaluation of Clavulanic Acid in Cats

Variable	Generic Mean	RLNAD Mean	Lower Bound	Upper Bound
AUC (µg/mL) *hour	6.87*	6.59*	99.8%	114.2%
C_{MAX} (µg/mL)	4.42*	4.30*	94.2%	113.8%
T_{MAX} (hour)	0.73†	0.72†	NA	NA

* Geometric Mean
† Arithmetic Mean

5. Conclusion:

   The generic amoxicillin trihydrate and clavulanate potassium 62.5 mg tablets are bioequivalent to CLAVAMOX 62.5 mg tablets in cats.

B. Bioequivalence Waiver

1. Objectives:

   The sponsor conducted two pivotal blood level bioequivalence studies and requested a biowaiver for the additional strength tablets (i.e., 62.5 mg, 250 mg, and 375 mg) to be used in dogs.

2. Test Facility:

   Kundl/Tirol, Austria

3. Dissolution Method and Validation:

   There is an USP monograph for amoxicillin trihydrate and clavulanate potassium tablets dissolution. The dissolution medium used in the USP method is water. The sponsor used three dissolution media with different pH values. Twelve vessels filled with test medium were placed into the dissolution apparatus. Test conditions are summarized as follows:

   - Dissolution medium:
     - 0.1 N hydrochloric acid, pH 1.2

    - Acetate buffer, pH 4.5
    - Phosphate buffer, pH 6.8
  - Volume in each vessel: 900 mL
  - Apparatus type: II, paddle
  - Rotation speed: 75 rpm
  - Temperature: 37 °C
  - Sampling time: 5, 10, 15, 30, and 45 minutes
  - Analytical method: HPLC with UV detection

All four strengths of amoxicillin trihydrate and clavulanate potassium tablets are dose proportional and made from a common blend. The reference and generic bio-lots used in the dog blood level bioequivalence study were the same lots used to support the dissolution profile comparisons.

The apparatus type, *in vitro* testing conditions, and sampling times were selected to make the dissolution method discriminatory, i.e., be able to detect significant differences between the dissolution profile of the test and reference drug products. Analytical method validation was performed to ensure that the quantification of drug concentration in all samples was accurate and precise.

To allow use of mean data in the calculation of similarity factor (f_2), the coefficient of variation should be less than 20% at the earlier time points (e.g., 5 minutes), and should be no greater than 10% at other time points. Only one data point beyond >85% dissolution was included in the calculation of the f_2. In comparing dissolution profiles, f_2 values ≥50 indicate sameness. In cases where tablets dissolved >85% within 15 minutes, a dissolution profile comparison using the f_2 test is unnecessary.

4. Results:

   a. 0.1 N hydrochloric acid (HCl), pH 1.2

      Amoxicillin dissolved ≥85% within 15 minutes in all strengths of the generic and RLNAD tablets. Because clavulanic acid degraded rapidly in 0.1 N HCl medium, the concentration of clavulanic acid decreased with time after 5 minutes. This medium was deemed unsuitable to be used for the comparative dissolution purpose.

   b. Acetate buffer, pH 4.5

      Amoxicillin and clavulanic acid dissolved ≥85% within 15 minutes in all strengths of the generic and RLNAD tablets.

   c. Phosphate buffer, pH 6.8

      Amoxicillin and clavulanic acid dissolved ≥85% within 15 minutes in 62.5 mg, 125 mg, and 250 mg generic and RLNAD tablets. For the generic 375 mg tablets, the dissolution profiles are not similar to that of the generic 125 mg bio-lot tablets (i.e. f_2<50). Therefore, the between-product comparison was performed.

The 125 mg generic tablet bio-lot is deemed similar to the 125 mg RLNAD bio-lot, because ≥85% dissolved within 15minutes. Similarity was demonstrated (i.e. f_2>50) by comparing the generic 375 mg tablets and the RLNAD 375 mg tablets. 24 vessels of each drug product were tested under this condition.

Table 5. Comparative Dissolution of 375 mg Generic and Reference Tablets

Compound	RLNAD vs. Generic
Amoxicillin	f_2 = 66
Clavulanic acid	f_2 = 83

5. Conclusions

Similarity is demonstrated between the generic and RLNAD drug products in all strengths in acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). A biowaiver can be granted for the generic 62.5 mg, 250 mg, and 375 mg amoxicillin trihydrate and clavulanate potassium tablets for use in dogs.

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 Amoxicillin Trihydrate and Clavulanate Potassium Tablets:

Veterinary Tablets
For Use in Dogs and Cats

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 Amoxicillin Trihydrate and Clavulanate Potassium Tablets, when used according to the label, are safe and effective.