Date of Approval: October 20, 2021

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-604

Amoxicillin and Clavulanate Potassium for Oral Suspension

Dogs and Cats

Amoxicillin and Clavulanate Potassium for Oral Suspension drops 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.

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*, *Pasteurella multocida*, and *Pasteurella* spp. Urinary tract infections (cystitis) due to susceptible strains of *E. coli*.

Sponsored by:

Dechra Veterinary Products LLC

Executive Summary

Amoxicillin and Clavulanate Potassium for Oral Suspension is approved to treat susceptible skin, soft tissue, and periodontal bacterial infections in dogs. Amoxicillin and Clavulanate Potassium for Oral Suspension is also approved to treat susceptible skin and soft tissue bacterial infections in cats, as well as urinary tract infections (cystitis) due to susceptible strains of *E. coli* in cats. The drug is a generic version of CLAVAMOX®.

	Proprietary Name	**Established Name**	**Application Type and Number**	**Sponsor**
Generic Animal Drug	Amoxicillin and Clavulanate Potassium for Oral Suspension	amoxicillin and clavulanate potassium for oral suspension	Abbreviated New Animal Drug Application (ANADA) 200-604	Dechra Veterinary Products LLC
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	CLAVAMOX®	amoxicillin and clavulanate potassium for oral suspension	New Animal Drug Application (NADA) 055-101	Zoetis Inc.

Amoxicillin and Clavulanate Potassium for Oral Suspension is given orally and made up of the broad-spectrum antibiotic amoxicillin trihydrate and the β-lactamase inhibitor clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin trihydrate has bactericidal activity against a variety of gram-positive and gram-negative, aerobic and anaerobic bacteria. However, the antibiotic can be inactivated by β-lactamases, so it isn't effective against bacteria that produce these enzymes. Clavulanic acid inhibits β-lactamase enzymes. By itself, clavulanic acid has only weak antibacterial activity, but when combined with amoxicillin trihydrate, it prevents bacteria that produce β-lactamases from destroying the antibiotic, thereby broadening the drug's spectrum of activity.

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.

Both the generic drug and RLNAD contain 50 mg of amoxicillin activity as the trihydrate and 12.5 mg of clavulanic acid activity as the potassium salt per mL. The sponsor conducted one *in vivo* blood-level study in dogs to show that Amoxicillin and

Clavulanate Potassium for Oral Suspension is bioequivalent to CLAVAMOX®. The sponsor also conducted one *in vivo* blood-level study in cats to show that Amoxicillin and Clavulanate Potassium for Oral Suspension is bioequivalent to CLAVAMOX® (amoxicillin and clavulanate potassium for oral suspension). No serious adverse events were reported during either study.

Conclusions
Based on the data submitted by the sponsor for the approval of Amoxicillin and Clavulanate Potassium for Oral Suspension, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-604

B. Sponsor

Dechra Veterinary Products LLC
7015 College Blvd., Suite 525
Overland Park, KS 66211

Drug Labeler Code: 017033

C. Proprietary Name

Amoxicillin and Clavulanate Potassium for Oral Suspension

D. Drug Product Established Name

amoxicillin and clavulanate potassium for oral suspension

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Suspension

G. Amount of Active Ingredient

Each mL of suspension contains 50 mg of amoxicillin activity as the trihydrate and 12.5 mg of clavulanic acid activity as the potassium salt.

H. How Supplied

22-mL bottles containing dry powder for reconstitution with water

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Dogs: The recommended dosage is 6.25 mg/lb (1 mL/10 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 (1 mL) twice a day. Skin and soft tissue infections such as abscesses and cellulitis/dermatitis should be treated for 5-7 days or 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 and Clavulanate Potassium for Oral Suspension drops 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.

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*, *Pasteurella multocida*, and *Pasteurella* spp. Urinary tract infections (cystitis) due to susceptible strains of *E. coli*.

N. Reference Listed New Animal Drug

CLAVAMOX®; amoxicillin and clavulanate potassium for oral suspension; NADA 055-101; Zoetis 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 in 30 healthy, fasted dogs and 40 healthy, fasted cats, respectively, to demonstrate product bioequivalence using the generic and RLNAD amoxicillin and clavulanate potassium oral suspensions, each containing 50 mg of amoxicillin activity as the trihydrate and

12.5 mg of clavulanic acid activity as the potassium salt per mL. The RLNAD is available in a powder for oral suspension, which, when reconstituted with 14 mL water, contains 50 mg of amoxicillin and 12.5 mg of clavulanic acid per mL. 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 generic and RLNAD products by applying the average bioequivalence approach to the 4 individual data sets generated in dogs and cats for both amoxicillin and clavulanic acid, as described in the Statistical Methods sections below.

A. Blood-level Bioequivalence Study in Dogs

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of amoxicillin and clavulanate potassium for oral suspension (50 mg/mL amoxicillin and 12.5 mg/mL clavulanic acid).

Title: Pivotal Bioequivalence Study Evaluating Dechra's Generic Amoxicillin Trihydrate/Clavulanate Potassium Suspension (62.5 mg/mL) vs. Clavamox® Drops (62.5 mg/mL) in Beagle Dogs. (Study No. D19001)

Study Dates: January 13, 2020 to January 6, 2021

Study Locations:

In-life phase: Auxvasse, MO

Bioanalytical testing: Nürnberg – Heroldsberg, Germany

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence for the generic Amoxicillin and Clavulanate Potassium for Oral Suspension and the RLNAD in fasted dogs.

Study Animals: 30 male dogs between 12.8 – 13.6 months of age and weighing 7.2 to 10.8 kg.

Experimental Design: A randomized, two-period, two-treatment, two-sequence crossover study using a two-stage sample size adaptive sequential design. The study was conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 0.1 mL per lb of body weight of either the generic or RLNAD according to their randomized treatment sequence (RLNAD/generic or generic/RLNAD).

Measurements and Observations: The plasma concentrations of amoxicillin and clavulanic acid 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:

Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC.

After Stage 1, a mixed-effect model was used to first evaluate futility. The model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. For both amoxicillin and clavulanic acid, the back-transformed upper and lower bounds of the 90% confidence interval on the test/reference ratio of means were calculated. Because all lower bounds were less than 1.11 and all upper bounds were greater than 0.90, the study was not stopped for futility. The power was then calculated at an α-level of 5% using the estimated intra-subject variance from the same statistical model described above and assuming a test/reference ratio of 0.90. Because the powers for clavulanic acid were lower than 80%, the bioequivalence at Stage 1 was evaluated using a two-one-sided test at the pre-specified α = 0.028, which translated into 94.4% confidence intervals for the test/reference ratio. Bioequivalence was established because the back-transformed estimated upper and lower bounds of the 94.4% confidence interval for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC were contained within the acceptance limits of 0.80 to 1.25. As seen in the tables below, C_{MAX} and AUC fall within the prescribed bounds (Tables II.1 and II.2). The mean values for time to maximum concentration (T_{MAX}) obtained for the generic and RLNAD were evaluated clinically.

Results:

As seen in Table II.1 and Table II.2 below, both AUC and C_{MAX} meet the bioequivalence criteria for amoxicillin and clavulanic acid in dogs.

Table II.1. Bioequivalence Evaluation of Amoxicillin in Dogs

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 94.4% CI	Upper 94.4% CI
AUC (µg/mL)*hour	22.57†	22.85†	0.99	0.94	1.04
C_{MAX} (µg/mL)	8.13†	8.31†	0.98	0.92	1.04
T_{MAX} (hours) (SD‡)	1.12 (0.26)‡	1.19 (0.35)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic:RLNAD
CI = confidence interval
NE = not estimated

Table II.2. Bioequivalence Evaluation of Clavulanic Acid in Dogs

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 94.4% CI	Upper 94.4% CI
AUC (µg/mL)*hour	6.27†	6.47†	0.97	0.87	1.08
C_{MAX} (µg/mL)	4.07†	4.21†	0.97	0.85	1.10

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 94.4% CI	Upper 94.4% CI
T_{MAX} (hours) (SD‡)	0.80 (0.26)‡	0.85 (0.39)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic:RLNAD
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 and RLNAD 62.5 mg/mL amoxicillin and clavulanate potassium oral suspensions are bioequivalent in dogs.

B. Blood-level Bioequivalence Study in Cats

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of amoxicillin and clavulanate potassium for oral suspension (50 mg/mL amoxicillin and 12.5 mg/mL clavulanic acid).

Title: A Randomized, Two-sequence, Four-Period Crossover Study to Evaluate the Bioequivalence of a Test Oral Suspension Formulation of Amoxicillin Trihydrate/Clavulanate Potassium Suspension (62.5 mg/mL) and a Commercially Available Reference Drug Product Clavamox® Drops, Zoetis (62.5 mg/mL) in 40 Fasted, Healthy Cats. (Study No. D20001)

Study Dates: August 6, 2020 to February 5, 2021

Study Locations:

In-life phase: Waverly, NY

Bioanalytical testing: Nürnberg – Heroldsberg, Germany

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence for the generic Amoxicillin and Clavulanate Potassium for Oral Suspension and the RLNAD in fasted cats.

Study Animals: 40 female cats between 10.8 months to 2.9 years of age and weighing 2.63 kg to 4.46 kg.

Experimental Design: A randomized, masked, four-period, two-sequence, single-dose crossover study. The study was conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 1.0 mL of either the generic or RLNAD according to their randomized treatment sequence (generic/RLNAD/generic/RLNAD or RLNAD/generic/RLNAD/generic).

Measurements and Observations: The plasma concentrations of amoxicillin and clavulanic acid 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:

Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC.

A mixed-effect model was used to evaluate bioequivalence of amoxicillin. The model included fixed effects of treatment, sequence and period, and random effects of set, and subject nested within sequence and set. Bioequivalence was established for amoxicillin 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 were contained within the acceptance limits of 0.80 to 1.25.

The mixed reference-scaled average bioequivalence approach (RSABE) was explored initially to evaluate the estimated within-subject standard deviation (s_{WR}) of the RLNAD data for clavulanic acid in cats. The s_{WR} of the RLNAD was calculated separately for transformed C_{MAX} and AUC, but based on FDA guidance, was below the threshold to use the RSABE approach for data analysis of clavulanic acid. Because the s_{WR} was less than 0.294 for both C_{MAX} and AUC (0.0878 and 0.1221, respectively), the average bioequivalence method was used to evaluate bioequivalence for clavulanic acid in cats. The statistical model included fixed effects of treatment, sequence and period, and random effects of set, and subject nested within sequence and set. Period was modeled as a repeated factor. Bioequivalence was established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence intervals for geometric mean ratio (generic:RLNAD) are contained within the acceptance limits of 0.80 to 1.25. As seen in the tables below, C_{MAX} and AUC fall within the prescribed bounds (Tables II.3 and II.4). The mean values for T_{MAX} obtained for the generic and RLNAD were evaluated clinically.

Results:

As seen in Table II.3 and Table II.4 below, both AUC and C_{MAX} meet the bioequivalence criteria for amoxicillin and clavulanic acid in cats.

Table II.3. Bioequivalence Evaluation of Amoxicillin in Cats

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 90% CI	Upper 90% CI
AUC (µg/mL)*hour	36.22†	37.41†	0.97	0.93	1.01
C_{MAX} (µg/mL)	9.59†	9.85†	0.97	0.94	1.01
T_{MAX} (hours) (SD‡)	1.29 (0.33)‡	1.24 (0.26)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic:RLNAD
CI = confidence interval
NE = not estimated

Table II.4. Bioequivalence Evaluation of Clavulanic Acid in Cats

Parameter	Generic Mean	RLNAD Mean	Ratio◇	Lower 90% CI	Upper 90% CI
AUC (µg/mL)*hour	10.29†	9.33†	1.10	1.07	1.14
C_{MAX} (µg/mL)	6.26†	5.68†	1.10	1.07	1.14
T_{MAX} (hours) (SD‡)	0.65 (0.21)‡	0.60 (0.19)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◇ Ratio = Generic:RLNAD
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 and RLNAD 62.5 mg/mL amoxicillin and clavulanate potassium oral suspensions are bioequivalent in cats.

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 Amoxicillin and Clavulanate Potassium for Oral Suspension:

For use in dogs and cats only.

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 Amoxicillin and Clavulanate Potassium for Oral Suspension, when used according to the label, is safe and effective for the indications listed in Section I.M. above.