

Date of Approval: April 23, 2021

FREEDOM OF INFORMATION SUMMARY
ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-702

Amoxicillin and Clavulanate Potassium Tablets
Dogs and Cats

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

Sponsored by:

Cronus Pharma Specialities India Private Ltd.

Executive Summary

Amoxicillin and Clavulanate Potassium Tablets are approved to treat susceptible skin and soft tissue infections and periodontal infections in dogs, and susceptible skin, soft tissue, and urinary tract infections in cats. The drug is a generic version of CLAVAMOX[®] (amoxicillin and clavulanate potassium tablets) Veterinary Tablets.

	Proprietary Name	Established Name	Application Type and Number	Sponsor
Generic Animal Drug	Amoxicillin and Clavulanate Potassium Tablets	amoxicillin and clavulanate potassium tablets	Abbreviated New Animal Drug Application (ANADA) 200-702	Cronus Pharma Specialities India Private Ltd.
Brand Name Animal Drug, also called the Reference Listed New Animal Drug (RLNAD)	CLAVAMOX [®]	amoxicillin and clavulanate potassium tablets	New Animal Drug Application (NADA) 055-099	Zoetis Inc.

Amoxicillin and Clavulanate Potassium Tablets are 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 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.

The sponsor conducted one *in vivo* blood-level study in fasted dogs to show that the 125 mg Amoxicillin and Clavulanate Potassium Tablets are bioequivalent to the 125 mg CLAVAMOX[®] Veterinary Tablets. The sponsor also conducted one *in vivo* blood-level study in fasted cats to show that the 62.5 mg Amoxicillin and Clavulanate Potassium Tablets are bioequivalent to the 62.5 mg CLAVAMOX[®] Veterinary Tablets. No serious adverse events were reported during either study.

The sponsor conducted one comparative *in vitro* dissolution study for the dog product. The dissolution profiles for the 62.5 mg, 250 mg, and 375 mg generic tablets were compared to the dissolution profile for the 125 mg generic tablet. The 125 mg generic tablet was used as the comparators for dogs, because that strength was shown to be bioequivalent to CLAVAMOX[®] Veterinary Tablets. All comparisons showed similar dissolution profiles. Therefore, the 62.5 mg, 250 mg, and 375 mg generic tablets for dogs qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). Therefore, FDA granted a biowaiver for these strengths.

User Safety

The labeling for Amoxicillin and Clavulanate Potassium Tablets includes a warning about allergic reactions to antimicrobial drugs, including penicillins, in sensitized people. The labeling also includes instructions for reducing the risk of allergic reactions in people when they handle such antimicrobial drugs.

Conclusions

Based on the data submitted by the sponsor for the approval of Amoxicillin and Clavulanate Potassium Tablets, 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 200-702

B. Sponsor

Cronus Pharma Specialities India Private Ltd.
Sy No-99/1, M/s GMR Hyderabad Aviation SEZ Ltd.
Mamidipalli Village, Shamshabad Mandal,
Ranga Reddy, Hyderabad, Telangana, 501218, India

Drug Labeler Code: 069043

U.S. Agent Name and Address:

Ms. Jodi Beaudry
Cronus Pharma LLC
2 Tower Center Boulevard
Suite 1101A
East Brunswick, NJ 00816

C. Proprietary Name

Amoxicillin and Clavulanate Potassium Tablets

D. Drug Product Established Name

amoxicillin and clavulanate potassium tablets

E. Pharmacological Category

Antibacterial

F. Dosage Form

Tablet

G. Amount of Active Ingredient

62.5 mg tablets (50 mg amoxicillin trihydrate, 12.5 mg clavulanic acid)

125 mg tablets (100 mg amoxicillin trihydrate, 25 mg clavulanic acid)

250 mg tablets (200 mg amoxicillin trihydrate, 50 mg clavulanic acid)

375 mg tablets (300 mg amoxicillin trihydrate, 75 mg clavulanic acid)

H. How Supplied

Each strength of Amoxicillin and Clavulanate Potassium Tablets is supplied in strip packs. Each carton holds 15 strips with 14 tablets per strip (210 tablets per carton).

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

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

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

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indications

Amoxicillin 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.

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 and clavulanate potassium tablets; NADA 055-099; Zoetis Inc.

II. BIOEQUIVALENCE

The FD&C Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTR) of 1988, allows for an abbreviated new animal drug application (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 to demonstrate product bioequivalence using the generic and RLNAD amoxicillin and clavulanate potassium tablets 62.5 mg tablet in cats and 125 mg tablet in dogs. The RLNAD is available in 62.5, 125, 250, and 375 mg tablet sizes. An *in vivo* blood-level study was conducted in 30 healthy, fasted cats. 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 62.5 mg CLAVAMOX[®] and the 62.5 mg generic Amoxicillin and Clavulanate Potassium Tablets by the average bioequivalence approach as described in the Statistical Methods section below.

Another *in vivo* blood-level study was conducted in 40 healthy, fasted dogs. The pivotal parameters to evaluate bioequivalence are the observed C_{MAX} and AUC from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX} . Bioequivalence was demonstrated between the 125 mg CLAVAMOX[®] and the 125 mg generic Amoxicillin and Clavulanate Potassium Tablets by the mixed reference-scaled average bioequivalence approach as described in the Statistical Methods section below.

A biowaiver for the generic 62.5 mg, 250 mg, and 375 mg tablets in dogs was requested. Dissolution data was used to demonstrate that the generic 62.5 mg, 250 mg, and 375 mg amoxicillin and clavulanate potassium tablets are comparable to the generic 125 mg tablet strength used in the dog *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 62.5 mg, 250 mg, and 375 mg Amoxicillin and Clavulanate Potassium Tablets in dogs was granted. The study information is summarized below.

A. 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 tablets (62.5 mg).

Title: Plasma Bioequivalence of Test and Reference Article Amoxicillin trihydrate/Clavulanate potassium Oral Tablets in the Cats. (Study No. 17.0566.002)

Study Dates: January 7, 2019 to January 8, 2020

Study Locations:

In-life phase: Waverly, NY

Bioanalytical testing: Andhra Pradesh, India

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 62.5 mg Amoxicillin and Clavulanate Potassium Tablets and the RLNAD 62.5 mg CLAVAMOX[®] in cats.

Study Animals: 30 male cats between 10 months to 2 years of age.

Experimental Design: A randomized, masked, two-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 62.5 mg of either the generic or RLNAD amoxicillin and clavulanate potassium tablets according to their randomized treatment sequence (generic/RLNAD or 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: The laboratory study was conducted as a single site, randomized, masked, two-period, two-sequence, two-treatment crossover design with a 14-day washout period between the two study periods. The enrolled 30 cats were housed in 3 rooms forming three cohorts, 10 cats in a room or cohort. In a given period, the dosing day for each cohort was offset by one day. Variables evaluated for bioequivalence are the C_{MAX} and area under the concentration curve from time 0 to the last value above the limit of quantitation and before the first value occurs below the limit of quantitation after C_{MAX} (AUC).

A mixed-effect model was used to evaluate bioequivalence for both analytes. The model included fixed effects of treatment, sequence and period, and random effects of cohort and animal nested within the sequence and cohort. Prior to the analysis, C_{MAX} and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90% confidence intervals for geometric mean ratios (generic:RLNAD) of both C_{MAX} and AUC of both analytes are contained within the acceptance limits of 0.80 to 1.25.

Results: As seen in the tables below, C_{MAX} and AUC fall within the prescribed bounds (Table II.1 and Table II.2). The mean values of time to maximum concentration (T_{MAX}) obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation of Amoxicillin in Cats

Variable	Generic Mean [†]	RLNAD Mean [†]	Ratio [◇]	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	21263.8	20797.8	1.02	0.86	1.22
C_{MAX} (ng/mL)	5022.3	4924.7	1.02	0.88	1.18
T_{MAX} (hr) (SD)	1.9 (0.5) [‡]	1.9 (0.5) [‡]	NE	NE	NE

[†] Geometric mean

[‡] Arithmetic mean and standard deviation (SD)

[◇] Ratio = Test/Reference

CI = confidence interval

NE = not estimated

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

Variable	Generic Mean [†]	RLNAD Mean [†]	Ratio [◇]	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	3035.7	2737.3	1.11	1.02	1.20
C _{MAX} (ng/mL)	1696.5	1538.9	1.10	0.99	1.23
T _{MAX} (hr) (SD)	0.8 (0.2) [‡]	0.7 (0.1) [‡]	NE	NE	NE

[†] Geometric mean

[‡] Arithmetic mean and standard deviation (SD)

[◇] Ratio = Test/Reference

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 62.5 mg Amoxicillin and Clavulanate Potassium Tablets and the RLNAD 62.5 mg tablets are bioequivalent in cats.

B. 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 tablets (125 mg).

Title: Plasma Bioequivalence of Test and Reference Article Amoxicillin trihydrate/Clavulanate potassium Oral Tablets in the Dog. (Study No. 17.0566.001)

Study Dates: August 13, 2018 to December 17, 2019

Study Locations:

In-life phase: Waverly, NY

Bioanalytical testing: Andhra Pradesh, India

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 125 mg Amoxicillin and Clavulanate Potassium Tablets and the RLNAD 125 mg CLAVAMOX[®] in dogs.

Study Animals: 40 female dogs between 13 months and 3 years of age.

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 125 mg of either the generic or RLNAD amoxicillin and clavulanate potassium tablets 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: The laboratory study was conducted as a single site, randomized, masked, four-period, two-sequence, two-treatment crossover design with a 14-day washout period between two adjacent periods. The enrolled 40 female dogs were housed in 2 rooms forming two cohorts, 20 dogs in a room or cohort. In a given period, the dosing day for each cohort was offset by one day. Variables evaluated for bioequivalence are the C_{MAX} and area under the concentration curve from time 0 to the last value above the limit of quantitation and before the first value occurs below the limit of quantitation after C_{MAX} (AUC).

The average bioequivalence method was used to evaluate bioequivalence for amoxicillin and the mixed reference-scaled average bioequivalence (RSABE) approach was used to evaluate bioequivalence for clavulanic acid. Prior to the analysis, C_{MAX} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (S_{WR}) of the RLNAD was calculated separately for transformed C_{MAX} and AUC to select the appropriate analysis approach based on the FDA guidance.

- For amoxicillin, the S_{WR} was less than 0.294 for both C_{MAX} and AUC, so the average bioequivalence method was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and cohort and animal within sequence and cohort as random effects. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratio (generic:RLNAD) is contained within the acceptance limits of 0.80 to 1.25.
- For clavulanic acid, the S_{WR} was equal to or greater than 0.294 for both C_{MAX} and AUC, so the RSABE method was used and bioequivalence was established based on the following two criteria:
 - The estimated 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta * \sigma_{WR}^2$ is less than zero (0), where μ_T and μ_R are the population means of the natural log transformed primary variable for the generic article and RLNAD, respectively, σ_{WR} is the population with-in subject standard deviation for RLNAD, $\theta = (\log(1.25)/\sigma_{wo})^2$ and $\sigma_{wo} = 0.25$.
 - The point estimate of the generic to RLNAD geometric mean ratio is contained within the acceptance limits of 0.80 and 1.25.

Results: As seen in Table II.3 and Table II.4 below, both AUC and C_{MAX} meet the bioequivalence criteria for both components.

Table II.3. Bioequivalence Evaluation of Amoxicillin in Dogs

Variable	Generic Mean [†]	RLNAD Mean [†]	Ratio [◇]	Lower 90% CI	Upper 90% CI
AUC (ng/mL)*hour	25982.3	27140.1	0.96	0.91	1.0
C _{MAX} (ng/mL)	8689.8	8999.5	0.97	0.92	1.01
T _{MAX} (hr) (SD)	1.3 (0.3) [‡]	1.4 (0.4) [‡]	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 Dogs

Variable	Generic Mean [†]	RLNAD Mean [†]	Point Estimate	95% Upper Confidence Bound
AUC (ng/mL)*hour	NE	NE	0.97	-0.11
C _{MAX} (ng/mL)	NE	NE	0.99	-0.12
T _{MAX} (hr) (SD)	1.3 (0.3) [‡]	1.4 (0.4) [‡]	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 125 mg Amoxicillin and Clavulanate Potassium Tablets and the RLNAD 125 mg tablets are bioequivalent in dogs.

C. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted in cats using the 62.5 mg amoxicillin and clavulanate potassium tablet strength, and in dogs using the 125 mg amoxicillin and clavulanate potassium tablet strength. A biowaiver for the generic 62.5 mg, 250 mg, and 375 mg tablets in dogs was requested. To qualify for a biowaiver for each of these product strengths, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic 62.5 mg, 250 mg, and 375 mg amoxicillin and clavulanate potassium tablets in dogs. The similarity factor (f_2) calculation was not used as all tablets dissolved > 85% in ≤ 15 minutes.

Comparisons were made between the following tablets for use in dogs:

- Generic 125 mg and generic 62.5 mg tablets
- Generic 125 mg and generic 250 mg tablets
- Generic 125 mg and generic 375 mg tablets

The objective was to demonstrate sameness between the generic 125 mg tablet strength and the generic 62.5 mg, 250 mg, and 375 mg amoxicillin and clavulanate potassium tablet strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: Water
- Dissolution medium volume: 900 mL
- Temperature: 37 °C
- Paddle speed: 75 rpm
- Number of vessels: 12
- Data points: 10, 15, 20, 30 and 45 minutes

The generic drug lot number used in the *in vivo* bioequivalence study was the same lot 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.

Because all tablets achieved 85% dissolution in ≤ 15 minutes, the use of the f_2 metric is not necessary.

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 62.5 mg, 250 mg, and 375 mg amoxicillin and clavulanate potassium tablets is granted.

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 Tablets:

Not for human use. Keep this and all drugs out of reach of children. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including amoxicillin and clavulanate potassium, are advised to avoid direct contact of the product with the skin and mucous membranes.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the Federal Food, Drug, and Cosmetic Act. The data demonstrate that Amoxicillin and Clavulanate Potassium Tablets, when used according to the label, is safe and effective for the indications listed in Section I.M. above.