Date of Approval: February 22, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-749

Kesium®

(amoxicillin and clavulanate potassium tablets)

Chewable tablet

Dogs and cats

Kesium® Chewable 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. Kesium® has 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:

Ceva Sante Animale

Executive Summary

Kesium® (amoxicillin and clavulanate potassium tablets) is approved for the following indications:

> *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. Kesium® has 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.*

The reference listed new animal drug (RLNAD) is CLAVAMOX® CHEWABLE (amoxicillin and clavulanate potassium tablets) sponsored by Zoetis Inc. under NADA 055-099.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in cats to show that the 62.5 mg Kesium® is bioequivalent to the 62.5 mg CLAVAMOX® CHEWABLE. Only the 62.5 mg tablet strength is approved for use in cats. No serious adverse events were reported during the study. The sponsor also conducted one *in vivo* blood-level study in dogs to show that the 125 mg Kesium® is bioequivalent to the 125 mg CLAVAMOX® CHEWABLE. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strengths approved for use in dogs. Based on the dissolution data, the 62.5 mg, 250 mg, and 375 mg tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver) in dogs. FDA granted a biowaiver for these strengths.

Conclusions

Based on the data submitted by the sponsor for the approval of Kesium®, 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 200-749

B. Sponsor

Ceva Sante Animale
10 Avenue de la Ballastière
33500 Libourne, France

Drug Labeler Code: 013744

C. Proprietary Name

Kesium®

D. Drug Product Established Name

amoxicillin and clavulanate potassium tablets

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

62.5 mg tablets (50 mg of amoxicillin activity and 12.5 mg of clavulanic acid)
125 mg tablets (100 mg of amoxicillin activity and 25 mg of clavulanic acid)
250 mg tablets (200 mg of amoxicillin activity and 50 mg of clavulanic acid)
375 mg tablets (300 mg of amoxicillin activity and 75 mg of clavulanic acid)

H. How Supplied

62.5 mg and 125 mg tablets: cartons holding 10 foil blister cards with 10 tablets each (100 tablets per carton)

250 mg and 375 mg tablets: cartons holding 12 foil blister cards with 8 tablets each (96 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.

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. Indication

Kesium® Chewable 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. Kesium® has 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® CHEWABLE; amoxicillin and clavulanate potassium tablets; NADA 055-099; Zoetis Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) 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. One study was in cats, and the other study was in dogs. The 62.5 mg tablet was used in the cat study, and the 125 mg tablet was used in the dog study. The RLNAD is available in 62.5, 125, 250, and 375 mg tablet sizes. The cat *in vivo* blood-level study was conducted in thirty-four 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 RLNAD amoxicillin and clavulanate potassium tablets and the 62.5 mg generic amoxicillin and clavulanate potassium tablets by the mixed reference-scaled average bioequivalence approach as described in the Statistical Methods section below.

The dog *in vivo* blood-level study was conducted in twenty-two healthy, fasted dogs. 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 125 mg RLNAD amoxicillin and clavulanate potassium tablets 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 waiver from the requirement to demonstrate *in vivo* bioequivalence (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

Title: Pivotal Bioequivalence Study of CLAVAMOX® Chewable and C662 When Administered Orally to Cats. (Study No. US/BEQ/C662/2003)

Study Dates: October 26, 2020 to September 17, 2021

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Middleton, WI

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 Kesium® (amoxicillin and clavulanate potassium tablets) and the RLNAD 62.5 mg CLAVAMOX® CHEWABLE (amoxicillin and clavulanate potassium tablets) in fasted cats.

Study Animals: 34 male and female domestic shorthair cats, approximately 10.5 months to 5 years of age

Experimental Design: A randomized, masked, four-period, two-sequence, single-dose crossover study 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/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 randomized, masked four-period, two-sequence, two-treatment, single-dose crossover design using 34 cats with a 14-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

The reference-scaled average bioequivalence approach (RSABE) was used as appropriate to evaluate bioequivalence through the mixed scaling approach. 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 FDA Guidances.

- The s_{WR} was less than 0.294 for both C_{MAX} and AUC for amoxicillin, so the average bioequivalence method was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Period was modeled as a repeated factor. Bioequivalence for amoxicillin was established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratios (generic:RLNAD) were contained within the acceptance limits of 0.80 to 1.25.

- The s_{WR} was equal to or greater than 0.294 for C_{MAX} and AUC for clavulanic acid, so the RSABE method was used, and bioequivalence was established based on the following two criteria:

- The estimated 95% upper confidence bound for $(\mu_T-\mu_R)^2- \theta^*\sigma^2_{WR}$ 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, $\theta = (\log (1.25)/\sigma_{W0})^2$ and $\sigma_{W0} = 0.25$.

- 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 the table below, C_{MAX} and AUC for amoxicillin fall within the prescribed bounds (Table II.1.). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation for Amoxicillin

Parameter	Generic Mean	RLNAD Mean	Ratio◊	Lower 90% CI	Upper 90% CI
AUC (hr*ng/mL)	36004.5†	37605.3†	0.96	0.91	1.0
C_{MAX} (ng/mL)	8695.8†	9130.7†	0.95	0.91	1.0
T_{MAX} (hours) (SD)‡	2.2 (0.9)‡	2.2 (0.8)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
CI = confidence interval
NE = not estimated

As seen in the table below, C_{MAX} and AUC for clavulanic acid fall within the prescribed bounds (Table II.2.). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.2. Bioequivalence Evaluation for Clavulanic Acid

Parameter	S_{wr}#	Generic Mean	RLNAD Mean	Ratio◊	Upper 95% Bound$
AUC (hr*ng/mL)	0.57	3718.2†	4390.9†	0.85	-0.087
C_{MAX} (ng/mL)	0.56	2304.0†	2586.1†	0.90	-0.129
T_{MAX} (hour) (SD‡)	NE	1.0 (0.4) ‡	1.1 (0.5) ‡	NE	NE

#Estimated within-subject standard deviation of the RLNAD
$Estimated 95% upper confidence bound of $(\mu_T-\mu_R)^2-\theta^*\sigma^2_{WR}$
† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
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 Kesium® (amoxicillin and clavulanate potassium tablets) and the RLNAD 62.5 mg CLAVAMOX® CHEWABLE (amoxicillin and clavulanate potassium tablets) are bioequivalent in cats.

B. Blood-level Bioequivalence Study in Dogs

Title: Pivotal Bioequivalence Study of CLAVAMOX® Chewable and C662 When Administered Orally to Dogs. (Study No. US/BEQ/C662/2006)

Study Dates: April 1, 2021 to December 21, 2021

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Middleton, WI

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 125 mg Kesium® (amoxicillin and clavulanate potassium tablets) and the RLNAD 125 mg CLAVAMOX® CHEWABLE (amoxicillin and clavulanate potassium tablets) in fasted dogs.

Study Animals: 22 intact male beagle dogs, approximately 15 months to 4 years of age

Experimental Design: A randomized, masked, four-period, two-sequence, single-dose crossover study 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 randomized, masked four-period, two-sequence, two-treatment, single-dose crossover design using 22 dogs with a 7-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. T_{MAX} was summarized and evaluated clinically.

The reference-scaled average bioequivalence approach (RSABE) was used as appropriate to evaluate bioequivalence through the mixed scaling approach. 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 FDA Guidances.

- The s_{WR} was less than 0.294 for both C_{MAX} and AUC for amoxicillin, so the average bioequivalence method was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Period was modeled as a repeated factor, with treatment as the group option and animal as the subject option. Bioequivalence for amoxicillin was established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratios (generic:RLNAD) were contained within the acceptance limits of 0.80 to 1.25.

- The s_{WR} was equal to or greater than 0.294 for C_{MAX} and AUC for clavulanic acid, so the RSABE method was used, and bioequivalence was established based on the following two criteria:

    - The estimated 95% upper confidence bound for $(\mu_T-\mu_R)^2- \theta^*\sigma^2_{WR}$ 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, $\theta = (\log (1.25)/\sigma_{W0})^2$ and $\sigma_{W0} = 0.25$.

    - 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 the table below, C_{MAX} and AUC for amoxicillin fall within the prescribed bounds (Table II.3.). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.3. Bioequivalence Evaluation for Amoxicillin

Parameter	Generic Mean	RLNAD Mean	Ratio◊	Lower 90% CI	Upper 90% CI
AUC (hr*ng/mL)	21414.0†	20801.9†	1.03	0.98	1.08
C_{MAX} (ng/mL)	7564.3†	7398.3†	1.02	0.95	1.10
T_{MAX} (hours) (SD)‡	1.4 (0.5)‡	1.50 (0.4)‡	NE	NE	NE

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
CI = confidence interval
NE = not estimated

As seen in the table below, C_{MAX} and AUC for clavulanic acid fall within the prescribed bounds (Table II.4.).

Table II.4. Bioequivalence Evaluation for Clavulanic Acid

Parameter	S_{WR}[#]	Generic Mean	RLNAD Mean	Ratio[◊]	Upper 95% Bound[$]
AUC (hr*ng/mL)	0.53	3575.3[†]	3741.3[†]	0.96	-0.139
C_{MAX} (ng/mL)	0.48	2555.0[†]	2585.1[†]	0.99	-0.118
T_{MAX} (hours) (SD)[‡]	NE	1.0 (0.4)[‡]	1.0 (0.3)[‡]	NE	NE

[†] Geometric mean
[‡] Arithmetic mean and standard deviation (SD)
[◊] Ratio = Test/Reference
NE = not estimated
[#] Estimated within-subject standard deviation of the RLNAD
[$] Estimated 95% upper confidence bound of $(\mu_T-\mu_R)^2- \theta*\sigma^2_{WR}$

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 125 mg Kesium® (amoxicillin and clavulanate potassium tablets) and the RLNAD 125 mg CLAVAMOX® CHEWABLE (amoxicillin and clavulanate potassium tablets) are bioequivalent in dogs.

C. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 125 mg amoxicillin and clavulanate potassium tablets strength in dogs. 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. Comparisons were made between the following tablets:

- 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 satisfy sameness between the generic 125 mg tablet strength used in the *in vivo* dog bioequivalence study and the 62.5 mg, 250 mg, and 375 mg generic tablet strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: Water
- Dissolution medium volume: 900 mL
- Temperature: 37 °C ± 0.5 °C
- Paddle speed: 75 rpm
- Number of vessels: 12
- Data points: 5, 10, 15, 30, and 45 minutes

The generic drug lot number used in the dog *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.

The use of mean data was not necessary since all profiles were rapidly dissolving and f_2 (similarity factor) calculations were not applicable.

A summary of the results is presented in Table II.5 below:

Table II.5. Similarity Results

Dissolution Comparison	Similarity Results
125 mg generic to the 62.5 mg generic	> 85% dissolved within 15 minutes supports sameness, f_2 not required
125 mg generic to the 250 mg generic	> 85% dissolved within 15 minutes supports sameness, f_2 not required
125 mg generic to the 375 mg generic	> 85% dissolved within 15 minutes supports sameness, f_2 not required

Study results demonstrate similar dissolution profiles for all comparisons. However, because of rapid dissolving characteristics (> 85% in 15 minutes) in all strengths, 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 value is ≥ 50, the product strengths used in the comparison qualify for a biowaiver. 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 Kesium®:

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 FD&C Act. The data demonstrate that Kesium®, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.