Date of Approval: June 16, 2012

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-326

RILEXINE Chewable Tablets

(cephalexin)
Dogs

For the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *Staphylococcus pseudintermedius.*

Sponsored by:

Virbac AH, Inc.

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## I. GENERAL INFORMATION:

| | |
|---|---|
| **A. File Number:** | NADA 141-326 |
| **B. Sponsor:** | Virbac AH, Inc.<br>3200 Meacham Blvd.<br>Fort Worth, TX 76137<br><br>Drug Labeler Code: 051311 |
| **C. Proprietary Name:** | RILEXINE Chewable Tablets |
| **D. Established Name:** | Cephalexin |
| **E. Pharmacological Category:** | Antimicrobial |
| **F. Dosage Form:** | Chewable Tablets |
| **G. Amount of Active Ingredient:** | RILEXINE tablets are supplied in four tablet sizes containing 75 mg, 150 mg, 300 mg, or 600 mg of cephalexin. |
| **H. How Supplied:** | RILEXINE tablets are available as chewable, bisected tablets, supplied in 75 mg, 150 mg, 300 mg, or 600 mg tablets packaged in bottles of 100 and 500 tablets or boxes of 28 blister-packs, 7 tablets per blister pack. |
| **I. How Dispensed:** | Rx |
| **J. Dosage:** | The recommended dose of RILEXINE (cephalexin) tablets is 22 mg/kg (10 mg/lb) of body weight twice daily for 28 days. |
| **K. Route of Administration:** | Oral |
| **L. Species/Class:** | Dogs |
| **M. Indication:** | RILEXINE tablets are indicated for the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *Staphylococcus pseudintermedius.* |

## II. EFFECTIVENESS:

### A. Dosage Characterization:

RILEXINE is indicated for the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *Staphylococcus pseudintermedius.*

RILEXINE is readily and nearly completely absorbed following oral administration (90% absolute bioavailability). Blood concentrations are proportional to dose within the range of at least 15 to 45 mg/kg. Binding to canine plasma proteins is low, ranging from 9 to 13% for concentrations of 0.5 to 100 µg/mL.

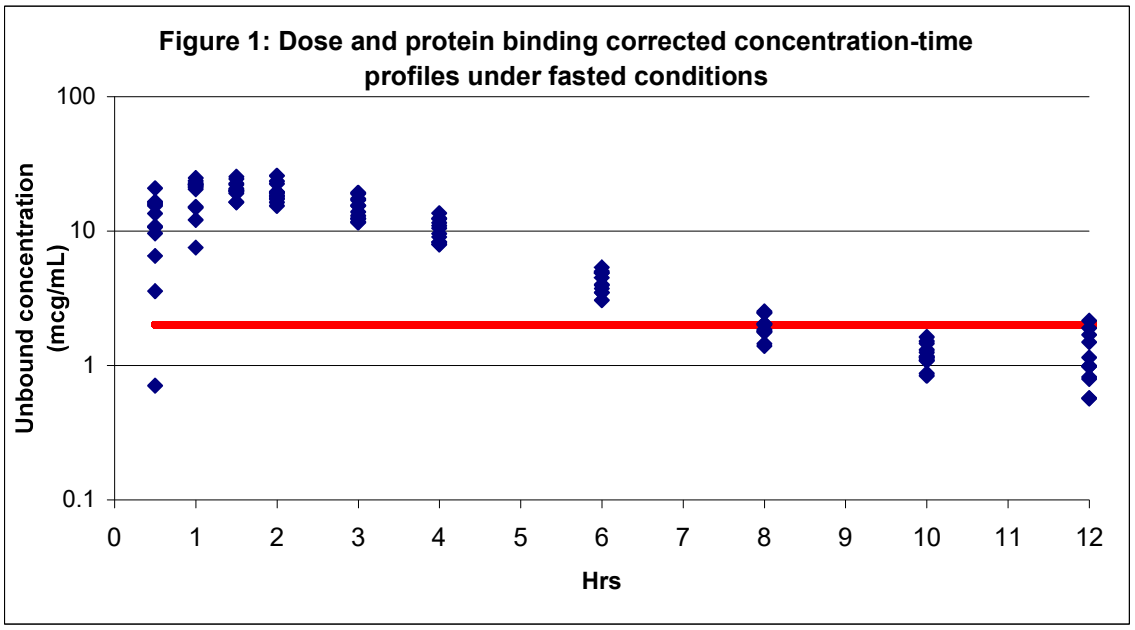
Food reduces the peak cephalexin concentrations, but has negligible influence on the extent of absorption. A summary of the pharmacokinetics observed in fed and fasted beagle dogs administered a single 22 mg/kg dose is provided in Table 1.

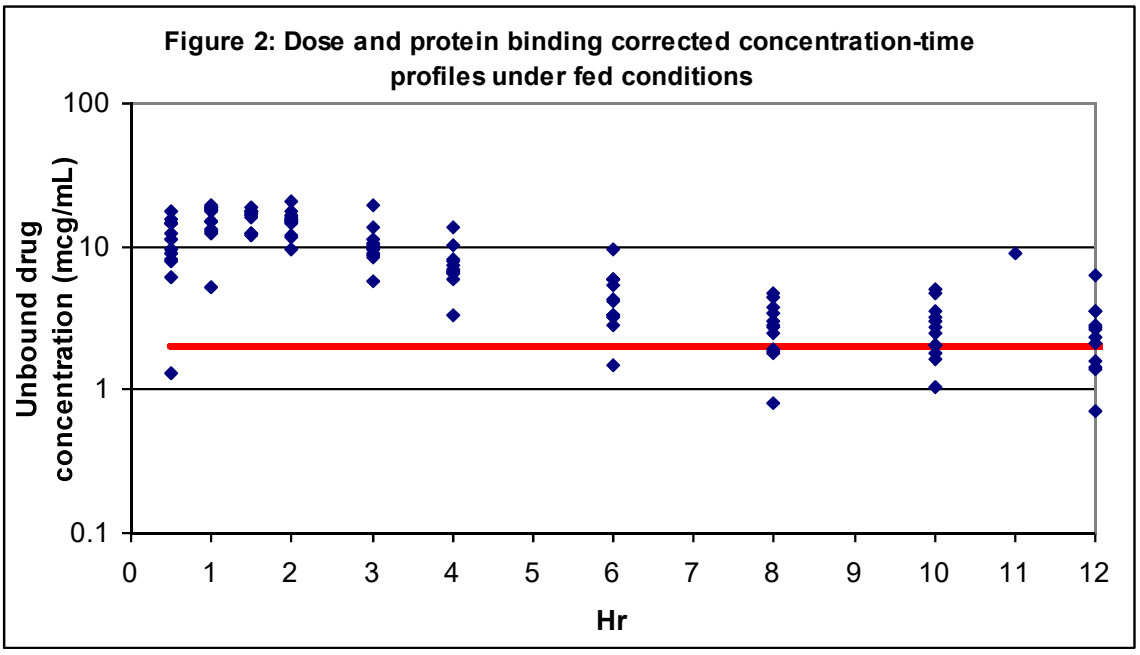
**Table 1: Pharmacokinetics parameter values (mean ± standard deviation), protein corrected in fasted and fed dogs following a single administration of 22 mg/kg dose of RILEXINE Chewable Tablets (N=12)**

| Parameter | FASTED Mean ± SD[1] | FED Mean ± SD[1] |
|---|---|---|
| AUCINF_obs (mg.h/L) | 105.36 ± 17.31 | 108.35 ± 25.85 |
| AUClast (mg.h/L) | 97.33 ± 13.18 | 95.19 ± 11.84 |
| Cmax (mg/L) | 21.66 ± 2.74 | 16.99 ± 2.71 |
| $T_{1/2}$ (h) | 7.33 ± 4.3 | 8.79 ± 6.44 |
| Tmax (h) | 1.42 ± 0.42 | 1.17 ± 0.25 |

[1]SD = Standard Deviation

Cephalosporins are associated with time-dependent killing effects. Accordingly, the pharmacodynamic (PD) target is time above MIC (T>MIC). For staphylococcal infections, the goal for time above MIC is 40% of the dosing interval which translates to 4.8 hrs for a BID dosing schedule. The blood levels obtained in 12 beagle dogs following a single 22 mg/kg dose under fed and fasted conditions are provided in Figures 1 and 2. To assess whether or not the PK-PD target is met with a 22 mg/kg BID dosing regimen under fed and fasted conditions, it was assumed that that the $MIC_{90}$ for *S. pseudintermedius* is 2 µg/mL. Plasma drug concentrations were normalized to exactly a 22 mg/kg dose and corrected for 10% protein binding (protein binding observed in canine plasma). Thus, under both fed and fasted conditions, the PK/PD target for *S. pseudintermedius* was met in all dogs after the first dose.




Duration of dosing was supported by a European clinical field effectiveness study conducted in dogs which evaluated a non-palatable formulation of RILEXINE.[1] In this study, dogs with superficial pyoderma were administered either RILEXINE at a dose of 15 mg/kg twice daily or SYNULOX (amoxicillin/clavulanic acid) at a dose of 12.5 mg/kg twice daily until total disappearance of lesions plus 10 days, not to exceed 2 months. The effectiveness of RILEXINE was compared to that of SYNULOX. Out of 53 interpretable cases, 22 of 24 (91.7%) in the RILEXINE group and 21 of 29 (72.4%) in

[1] The bioequivalence of the non-palatable formulation and the palatable formulation intended for marketing was demonstrated in a subsequent in vivo blood level bioequivalence trial.

the SYNULOX group were free of cutaneous lesions after treatment. The difference in effectiveness between groups was not statistically significant ($p>0.05$). The average recovery time for dogs in the RILEXINE group was 27.7 ± 15 days. The average recovery time in the SYNULOX group was 35.3 ± 18.5 days. The difference between the times to recovery for both groups was not statistically significant ($p>0.05$).

**B. Substantial Evidence:**

1. Type of Study: Field study

   a. Title: "Field effectiveness and safety of 646.06 (cephalexin) for the treatment of secondary superficial bacterial pyoderma in dogs" Study # U-646.060000-30004.

   b. Type of Study: Field Effectiveness Study

   c. Study Dates: October 2008-June 2010

   d. Investigators:

   Dr. Susan Baker
   West Palm Beach, FL

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   Tampa, FL

   e. Study Design: The study was a two-group, parallel, multicenter, placebo-controlled, blinded, and randomized clinical field effectiveness study in naturally afflicted dogs.

1) Objective: The objective of this clinical study was to evaluate the effectiveness and safety of RILEXINE (cephalexin) Chewable Tablets for the treatment of secondary superficial bacterial pyoderma in dogs when administered orally at 22 mg/kg (10 mg/lb) body weight, twice daily.

2) Study Animals: Two hundred and eleven (211) dogs with clinical signs of canine secondary superficial bacterial pyoderma were enrolled. This included dogs of all ages, both sexes, and many different breeds and mixes.

3) Treatment Groups (Table 2): The animals were randomized into two treatment groups in a 2:1 ratio of RILEXINE tablets and non-vehicle control (placebo), respectively.

**Table 2. Treatment Groups**

| **Treatment Group** | **Dose** | **Number of dogs enrolled (# evaluable)** |
|---|---|---|
| RILEXINE Chewable Tablet | 22 mg/kg (10 mg/lb) twice daily orally for 28 days | 145 (91) |
| Placebo | Twice daily for 28 days | 66 (40) |
| Total | | 211 (131) |

4) Administration: The dosage of the RILEXINE Chewable Tablets was 22 mg cephalexin per kg body weight (10 mg/lb) twice a day for 28 days, administered orally. The placebo tablets were administered orally, twice daily, in the same manner as the RILEXINE Chewable Tablets. Test article (RILEXINE or placebo control) was dispensed at each study visit, in quantities sufficient to permit twice daily dosing for nine days, based on the animal's body weight at the visit. Pet owners were instructed to administer the product twice daily without regard to food.

5) Dosage Form:
RILEXINE:
Final market formulation of RILEXINE Chewable Tablet was presented as chewable, bisected tablets, supplied in four tablet sizes containing 75 mg, 150 mg, 300 mg, or 600 mg of cephalexin.

Placebo
The control product was a non-vehicle, scored placebo tablet, manufactured to appear similar to RILEXINE, and provided in four tablet sizes.

6) Measurements and Observations:
Clinical parameters (papules, pustules, and/or folliculitis) were observed and recorded during physical exams at each weekly visit, and microbiological cultures of active pyoderma lesions were obtained at enrollment and, if applicable, upon withdrawal/failure.

Samples for clinical chemistries, hematology, and urinalysis were collected at enrollment and at week 5.

Inclusion criteria: Dogs enrolled in the study had clinically significant lesions of secondary superficial bacterial pyoderma characterized by a Moderate or Severe scoring of one or more of the following Primary Clinical Signs (PCS) at the time of enrollment: papules, pustules, and/or folliculitis. Scoring of the PCS was done on a 0-3 scale:

- 0 = (Absent) No clinical signs characteristic of superficial pyoderma present
- 1 = (Mild) 1 to 4 lesions per 100 $cm^2$
- 2 = (Moderate) 5 to 12 lesions per 100 $cm^2$
- 3 = (Severe) More than 12 lesions per 100 $cm^2$

Exclusion Criteria: Dogs not having a positive pre-treatment bacterial culture as well as dogs not scoring at least one Moderate or Severe rating in one of the primary clinical signs were excluded from the study. Dogs on systemic and/or topical antibiotics or short-acting corticosteroids within two weeks of enrollment, or long-acting corticosteroids within 90 days of enrollment, were excluded. Also, dogs with hypothyroidism (based on low $T_4$ values) were excluded from the study.

7) Assessment of Effectiveness: The success or failure of RILEXINE Chewable Tablet therapy was based on the Primary Clinical Scores and microbiological outcomes. The outcomes of the secondary signs, seborrhea, erythema, lesional spreading (except the first visit), and/or pruritus were used to further characterize treatment progression, but were not used to judge success or failure. Cases were evaluated individually for their response to treatment. A case was considered a treatment success if there were no lesions to culture at both the time treatment was stopped (Day 29, Visit 5) and one week later (Day 36, Visit 6). An animal was considered a treatment failure if the animal exited the study due to a lack of clinical improvement, or if the clinical signs (lesions) of pyoderma were still present at the time treatment was stopped or one week later (A PCS greater than 0 on Day 29 or Day 36 for papules, pustules, and/or folliculitis).

8) Assessment of Safety: Safety was evaluated by comparing the adverse reactions between the two treatment groups. The adverse reactions were evaluated by comparing the incidence of adverse reactions observed (percentage), duration, severity, and relationship to RILEXINE Chewable Tablets. Safety was also assessed by comparing urinalysis, CBC, and blood chemistry parameters between the two treatment groups.

f. Statistical Analysis: The outcome variable (treatment success or failure) was analyzed using a generalized linear model assuming a binomial distribution with a logit link function. Treatment group was a fixed effect in the model and site was a random effect. Continuous safety variables were analyzed separately using an analysis of covariance with

a one-way treatment structure with two levels (IVP or placebo) and measurements from the initial visit as the covariate.

g. Results: Of the 211 cases enrolled, randomized and dosed, 80 cases were excluded from the effectiveness evaluation. The most common reason for exclusion was negative bacterial culture results. Other reasons for exclusion were failure to meet inclusion criteria, dosing non-compliance, and missing or incomplete microbiology data.

1. Primary endpoint: Percentage cure in the effectiveness population is listed in Table 3.

**Table 3. Primary endpoint: Percentage of Cure* (Effectiveness population)**

| Treatment | RILEXINE Chewable Tablet | Placebo | p-value |
|---|---|---|---|
| N | 91 | 40 | |
| Success | 64 (70.3%) | 5 (12.5%) | 0.0009 |
| Failures | 27 | 35 | |

*Absence of lesions at the end of the study

At the end of the study, 70% of the dogs in the RILEXINE treatment group were considered a success, whereas 13% of dogs in the placebo treatment group were considered a success (p=0.0009).

2. Secondary endpoints: The PCS was repeatedly measured over the treatment period. At the end of treatment, the mean papules score was 1.55 (±1.35) for the placebo group and 0.37 (±0.84) for the RILEXINE group. At the end of treatment, the mean pustules score was 1.27 (±1.25) for the placebo group and 0.29 (±0.70) for the RILEXINE group. At the end of treatment, the mean folliculitis score was 1.61 (±1.19) for the placebo group and 0.39 (±0.91) for the RILEXINE group.

3. Safety: Although the means of several clinical chemistry and CBC parameters were significantly different between the two treatment groups at the end of the study, the differences were not clinically significant and the means of all parameters remained within the control range. As treatment progressed, skin and coat condition became more normal in the RILEXINE group compared to the placebo; there were no other differences noted between the two treatment groups during the physical examinations conducted during the study.

**Adverse reactions**: The most common adverse reactions in dogs included diarrhea, vomiting, anorexia, and lethargy. A total of 211 dogs were included in the field study safety analysis. The most common adverse reactions are summarized in Table 4.

**Table 4: Number of Dogs* with Adverse Reactions Reported During the Study with RILEXINE**

| ADVERSE REACTION | Rilexine n=145 | Placebo n=66 |
|---|---|---|
| Number of dogs with adverse reactions* | 50 (34%) | 22 (33%) |
| Vomiting | 29 | 9 |
| Diarrhea | 19 | 6 |
| Anorexia | 13 | 2 |
| Lethargy | 9 | 3 |
| Pruritus | 5 | 0 |
| Dermatitis | 4 | 3 |
| Skin Lesions | 5 | 1 |
| Otitis Externa | 4 | 2 |
| Polydipsia | 2 | 2 |
| Somnolence | 2 | 0 |
| Flatulence | 1 | 1 |
| Tachypnea | 1 | 1 |

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study

4. Microbiology*:* RILEXINE is a cephalosporin antibiotic**.** Like other β-lactam antimicrobials, RILEXINE exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalently binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall.

   Identification of bacterial pathogens was made to the species level, based on morphology, Gram stain, growth characteristics, standard individual biochemical testing, and/or commercially available identification test kits. Minimum inhibitory concentration (MIC) testing was conducted in accordance with applicable Clinical and Laboratory Standards Institute (CLSI) standards. RILEXINE MICs for the pre-treatment bacterial pathogens isolated from enrolled dogs are summarized in Table 5.

**Table 5: Summary of Cephalexin MIC values against *S. pseudintermedius* isolates from 88 dogs treated with Rilexine for bacterial pyoderma in a US field study during 2008-2009.**

| Microbial Treatment Outcome | Time of Sampling | $MIC_{50}$ µg/mL | $MIC_{90}$ µg/mL | MIC Range µg/mL |
|---|---|---|---|---|
| Success (n= 61)* | Pre-treatment | 1 | 2 | 1-2 |
| Failure (n=27) ** | Pre-treatment | 1 | 2 | 1-8 |
| | Post-treatment (n=17) | 2 | 16 | 1-32 |

* No post-treatment sampling was conducted due to the absence of lesions

** Of the 27 failures, 10 did not have positive post-treatment cultures

h. Conclusions: RILEXINE Chewable Tablets administered orally at a dose of 22 mg/kg (10 mg/lb) body weight, twice daily, was effective for the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *Staphylococcus pseudintermedius* and was well tolerated by the study population.

## III. TARGET ANIMAL SAFETY:

### A. Drug Tolerance Study of Cephalexin Tablets in Dogs:

1. Type of Study: Laboratory safety study (conducted per GLP)

2. Study Director: Zac Lloyd, B.S.
Mattawan, MI

3. General Design:

a. Purpose: The objective of the study was to evaluate the safety of RILEXINE Chewable Tablets when administered orally, three times a day, to young, healthy Beagles at 1, 3, and 5 times the proposed target dose (22 mg/kg) for 12 weeks and twice a day at the 1X dose (22 mg/kg) for 12 weeks.

b. Test Animals: Forty healthy Beagles (20 M and 20 F), 12 weeks of age at the first treatment (weighing 3.4 to 5.9 kg at randomization), were randomly assigned to the control group or the RILEXINE treatment groups (four/sex/group).

c. Control: placebo tablets

d. Dosage form: The final market formulation of cephalexin was administered. There are four tablet sizes containing 75, 150, 300, and 600 mg of cephalexin.

e. Route of administration: Oral

f. Dosages used:
**Table 1. Dose Groups**

| Group | Dose | Number and Sex of Dogs |
|---|---|---|
| 1 | 0 mg/kg TID | 4 M, 4 F |
| 2 | 22 mg/kg TID (1X) | 4 M, 4 F |
| 3 | 66 mg/kg TID (3X) | 4 M, 4 F |
| 4 | 110 mg/kg TID (5X) | 4 M, 4 F |
| 5 | 22 mg/kg BID | 4 M, 4 F |

g. Test duration: Twelve weeks

h. Variables measured: Clinical examinations, fecal examinations, observations, and physical examinations were assessed pre-test and throughout the course of the study. Body weights were measured pre-test and during Weeks 2, 4, 6, 8, 10, and 12. Food consumption was measured weekly. Ophthalmic examinations were conducted pre-test and prior to study termination. Physical and neurological examinations were conducted pre-test and during Weeks 4, 8, and 12. Electrocardiographic examinations were conducted pre-test and after the first daily dose during the last week of dosing. Blood and urine samples for clinical pathology were evaluated pre-test and during Weeks 8 and 12. Plasma cephalexin concentrations were evaluated at designated timepoints pre-test and once prior to the first daily dosing during Weeks 4, 8, and 12. At study termination on Day 87, necropsy examinations were performed, organ weights measured, and histopathology examined.

4. Results: All dogs survived to termination of the study.

a. The most common clinical findings included epiphora, salivation, vomiting, and diarrhea among all the dose groups. Decreased activity was observed in one dog in the 22 mg/kg/twice a day group, one dog in the 22 mg/kg/three times a day group, and in one dog in the 66 mg/kg/three times a day group. These observations were mild and sporadic.

b. Hematology and serum chemistry: There were statistically significant increases in alanine aminotransferase (ALT) (pooled overall results) in the 110 mg/kg three times a day group ($P = 0.0246$) and in the 22 mg/kg twice a day group ($P = 0.0359$) that increased in a dose-dependent pattern. These changes were minimal and the values remained within expected historical control ranges. There was a statistically significant ($P = 0.0061$) increase in sorbitol dehydrogenase (SDH) in the 110 mg/kg three times a day group (pooled overall results) compared to the controls.

These changes were minimal and the values remained within expected historical control ranges. There were statistically significant decreases in total protein in the 110 mg/kg three times a day group (P = 0.0053), and/or globulin in the 22 (P = 0.0003), 66 (P = 0.0027), and 110 mg/kg (P = 0.0002) three times a day groups compared to the controls. These changes resulted in occasional statistically significant increases in albumin/globulin ratios. Although a drug effect cannot be ruled-out, these changes were mild and not clinically relevant.

c. Coagulation: A statistically significant (P = 0.0222) prolongation in prothrombin time (PT) was observed in the 22 mg/kg three times a day group (pooled results). This was not considered clinically relevant due to the small change which remained within the reference ranges.

d. Urinalysis: One dog in the 110 mg/kg three times a day group had moderate amounts of bilirubinuria at the Week 8 and Week 12 samplings. No clinical significance was noted.

e. Plasma analysis: Cephalexin was not present in any Day 1 samples prior to dosing or in any control animals. After dosing, cephalexin was well absorbed into systemic circulation of the treated dogs. Within gender and dosage level, Week 8 mean trough concentrations were generally higher than the Week 4 and 12 mean trough concentrations (between a 0.9 and 3.6-fold difference). The geometric mean plasma cephalexin trough concentration following three times daily administration of the 110 mg/kg dose was 11.2 mcg/mL compared to 2.6 mcg/mL and 8.7 mcg/mL following 22 mg/kg and 66 mg/kg, respectively at Week 12. Geometric mean plasma cephalexin trough concentrations following administration of 22 mg/kg twice daily were 0.7, 1.3, and 1.0 mcg/mL at Weeks 4, 8, and 12, respectively.

f. Gross Pathology and Histopathology: Macroscopic lesions were rare, and were considered incidental findings. Microscopic lesions were rare and were typical findings in dogs of this age and breed.

5. Conclusions: The daily oral administration of cephalexin tablets to young Beagles, three times a day at 1, 3, and 5 times the proposed dose (22 mg/kg), and twice a day at the proposed dose (22 mg/kg) for 12 weeks was well tolerated.

## IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 NADA.

## V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to RILEXINE tablets:

"For use in dogs only. Not for use in humans. Keep this drug out of the reach of children. Antimicrobials, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. Sensitive individuals handling such antimicrobials, including cephalexin, should avoid contact of the product with the skin and mucous membranes in order to minimize the risk of allergic reactions.

In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

To obtain a copy of the Material Safety Data Sheet (MSDS), or to report adverse reactions, call 1-800-338-3659."

## VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that RILEXINE, when used according to the label, is safe and effective for the treatment of secondary superficial bacterial pyoderma in dogs caused by susceptible strains of *Staphylococcus pseudintermedius.*

### A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose secondary superficial bacterial pyoderma and prescribe appropriate treatment.

### B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

### C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.