Date of Approval: November 7, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-344

VERAFLOX Oral Suspension for Cats

Pradofloxacin
Cats

For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and *Staphylococcus pseudintermedius.*

Sponsored by:

Bayer HealthCare LLC
Animal Health Division

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-344
B. Sponsor:	Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201 Drug Labeler Code: 000859
C. Proprietary Name:	VERAFLOX Oral Suspension for Cats
D. Established Name:	Pradofloxacin
E. Pharmacological Category:	Antibacterial
F. Dosage Form:	Oral suspension
G. Amount of Active Ingredient:	25 mg/mL
H. How Supplied:	15 mL vial, 30 mL vial
I. How Dispensed:	Rx
J. Dosage:	7.5 mg/kg (3.4 mg/lb) once daily for 7 consecutive days
K. Route of Administration:	Oral
L. Species/Class:	Cats
M. Indication:	VERAFLOX is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and *Staphylococcus pseudintermedius.*

II. EFFECTIVENESS:

A. Dosage Characterization:

SUMMARY: Pharmacokinetic/Pharmacodynamic (PK/PD) justification for the selection of a 7.5 mg/kg body weight oral dose is based upon predicted individual unbound serum pradofloxacin concentrations at steady state (fasted cats) and a minimum inhibitory concentration (MIC_{90}) of 0.12µg/mL. Because linear pharmacokinetics were confirmed within the range 2.5 to 10 mg/kg, the PK/PD metrics of AUC/MIC and Cmax/MIC following a 7.5 mg/kg dose were extrapolated from steady-state pharmacokinetics data generated with 2.5, 5, and 10 mg/kg doses of Pradofloxacin 2.5% w/v Cat Oral Suspension. The probability of attaining a certain PK/PD metric was based upon linear regression methods using the data generated by Daube, *et al.*, 2005 (Study 143866). It was concluded that free drug steady-state Cmax/MIC and AUC/MIC values predictive of product effectiveness will be achieved when an oral dose of 7.5 mg/kg body weight of the pradofloxacin suspension formulation is administered daily to fasted cats.

1. Study 143357. "Pharmacokinetics of Pradofloxacin 2.5% w/v Cat Oral Liquid and Pradofloxacin 15 mg Tablets in Fasted and Fed Cats after Single Oral Application at Dosages of 5 and 3 mg/kg Body Weight."

Twelve healthy adult male domestic shorthair cats, age range 11 to 12 months, received four treatments: 5 mg/kg body weight Pradofloxacin Cat Oral Suspension 2.5% (fasted), 5 mg/kg body weight Pradofloxacin Cat Oral Suspension 2.5% (fed), one Pradofloxacin Tablet 15 mg (fasted), and one Pradofloxacin Tablet 15 mg (fed), according to a four sequence, four-period crossover design. Each treatment period was separated by at least 14 days. Each cat was fasted overnight prior to treatment. Fasted cats were fed about five hours after treatment, and fed cats received food 20-40 minutes before treatment. Blood samples were collected at 1 day prior to each treatment and at 0.5, 1, 2, 4, 6, 10, 24, 30, and 48 hours after each treatment. Table 1 lists the summary statistics for the serum pradofloxacin concentrations and demonstrates that pradofloxacin oral bioavailability is significantly decreased in the presence of food.

Table 1. Mean (1 SD) serum pradofloxacin concentrations following 5 mg/kg dose of pradofloxacin 2.5% oral suspension.

Parameter	Fasted	Fed
Cmax (µg/L)	2116 (549)	999 (400)
Tmax (hr)	0.8	1.4
AUC_{0-24} (µg*hr/L)	9111 (1939)	6745 (1524)
AUC_{0-Last} (µg*hr/L)	9404 (2256)	6914 (1625)
Half-Life (hr)	7.3 (1.7)	6.4 (1.2)

2. Study 143866. "Serum Pharmacokinetics of Pradofloxacin 2.5% w/v Cat Oral Suspension after Daily Oral Administration at Dosages of 2.5, 5 and 10 mg/kg Body Weight on Five Successive Days in Cats."

Using a three sequence, three-period crossover design, twelve healthy adult male European shorthair cats, ages 11 to 12 months, received three treatments (2.5 mg/kg/day, 5 mg/kg/day, and 10 mg/kg/day body weight), each consisting of once daily administration of Pradofloxacin 2.5% Oral Suspension under fasted conditions for 5 consecutive days. Each cat was fasted overnight prior to treatment and for about five hours after treatment. Treatments were separated by at least 13 days. Blood samples were collected daily at hours zero (predose), 0.5, 1, and 24 hours post-dose. In addition, blood samples were collected at 2, 4, 6, and 10 hours post-dose on Treatment Days 1 and 5 and at 30, 48, and 72 hours following dose 5. As seen in Table 2, the mean Cmax and AUC values are proportional across doses following dose five, suggesting that pradofloxacin systemic exposure is linear between 2.5 and 10 mg/kg body weight. Minimal drug accumulation occurs with repeated administrations.

Table 2. Mean (1 SD) serum steady state pradofloxacin concentrations in fasted cats (Dose 5 of pradofloxacin 2.5% Oral Suspension).

Parameter	2.5 mg/kg Dose	5 mg/kg Dose	10 mg/kg Dose
Cmax (µg/L)	953 (172)	2159 (343)	3553 (712)
Tmax (hr)	0.6	0.7	0.8
AUC96-120 (µg * hr/L)	4491 (866)	8529 (1917)	16519 (3278)
Half-life (hr)	7.4 (2.2)	9.8 (3.3)	10.3 (3.8)
Observed AI[a]	1.04 (0.16)	1.22 (0.22)	1.08 (0.17)
Ratio[b]	0.95 (0.13)	1.13 (0.20)	1.00 (0.15)

[a]Observed Accumulation Index (AI) = $AUC96\text{-}120_{Dose\ 5}/AUC0\text{-}24_{Dose\ 1}$.
[b]Ratio = $AUC96\text{-}120_{Dose\ 5}/AUC0\text{-}inf_{Dose\ 1}$.

3. Study Report 27405. "Comparative Plasma Protein Binding of Pradofloxacin and Enrofloxacin in Cats."

Plasma samples were harvested from blood samples of 12 cats. The plasma protein binding determination was carried out using an ultrafiltration method. The results show a 30% binding of pradofloxacin to feline plasma proteins over the concentration range 150 to 1500 ng/mL.

CONCLUSIONS: Using the data generated in Study 143866, free pradofloxacin concentrations were calculated for each animal at 2.5, 5, and 10 mg/kg body weight dose-levels. Pradofloxacin pharmacodynamic data was obtained from Study 23321, "Study to Determine the In Vitro Susceptibility of Selected Canine and Feline Pathogens to Pradofloxacin and Five Other Antimicrobials." The majority of pathogens had a pradofloxacin MIC90 of ≤ 0.015-0.12 µg/mL (*Pasteurella multocida*, *Staphylococcus pseudintermedius*, and *Streptococcus spp*.). To predict

steady-state Cmax/MIC (Cmaxss/MIC) and AUC96-120/MIC (AUCss/MIC) mean values at 7.5 mg/kg, dose adjusted from the data generated with a 2.5 mg/kg, 5 mg/kg, and 10 mg/kg dose were analyzed with a least-squares linear regression method. Using the estimated linear regression parameters, the 95% Confidence Limits about the predicted steady-state mean CMAXss/MIC and mean AUCss/MIC values are 15.1 to 17.4 and 70.3 to 81.0, respectively, following a 7.5 mg/kg body weight daily dose. Therefore, the proposed pradofloxacin dose of 7.5 mg/kg body weight daily in fasted cats is justified.

B. Substantial Evidence:

1. Clinical Evaluation of the Efficacy and Safety of Pradofloxacin 2.5% Oral Suspension in the Treatment of Skin Infections (Wounds and Abscesses) in Cats. Bayer Study No: 151.562.

a. Type of Study: Multi-center field effectiveness study.

b. Objective: The objective of this multi-site, masked, negative-controlled, and randomized clinical field study was to demonstrate the effectiveness and safety of VERAFLOX Oral Suspension administered at 3.4 mg/lb (7.5 mg/kg) body weight once daily for 7 consecutive days for the treatment of skin infections (wounds and abscesses) in cats caused by relevant bacterial pathogens.

c. Investigators:

Dr. Gayle Sternefeld	Baltimore, MD
Dr. Richard Benjamin	Berkeley, CA
Dr. Wallace Diehl	Chapel Hill, NC (2 sites)
Dr. Dean Vicksman	Denver, CO
Dr. Jay Alan Butan	Lake Worth, FL
Dr. K.C. Brooks	Lodi, WI
Dr. David W. Knaak	Peoria, IL
Dr. Cathy Lund	Providence, RI
Dr. Renee Ziegler-Post	Quakertown, PA
Dr. Samuel Geller	Quakertown, PA
Dr. Susan P. Hubbard	Rochester, NY
Dr. William C. Campaigne	Seguin, TX
Dr. Dean Rund	Springfield, MO
Dr. Roger Sifferman	Springfield, MO
Dr. Victor Manoharan	West Palm Beach, FL

d. Study Design:

1) Study Animals: Two hundred eighty-two (282) cats were included in this study: 190 cats were assigned to the VERAFLOX Oral Suspension group and 92 to the placebo (vehicle without active ingredients) group. The age ranged from 0.3 to 19 years and body weight ranged from 3.6 to

27.3 pounds. The majority (247) were domestic shorthair cats.

2) Treatment Groups: Cats were randomly assigned to VERAFLOX or placebo in a 2:1 ratio as shown in Table 3. The majority of cases excluded from the effectiveness population were due to negative Day 1 culture (70 cats).

Table 3. Number of cases evaluated by population.

Populations	Total Cats	VERAFLOX Cats	Placebo (vehicle) Cats
Safety	282	190	92
Effectiveness	182	116	66

3) Enrollment criteria: Cats were eligible for the study if they were at least 12 weeks of age with an infected wound or abscess.

The wound or abscess was assessed using a wound scoring system that evaluated five clinical parameters (soft tissue swelling and edema, erythema, heat, pain, and discharge), each on an individual scale of 0 – 2, with 2 being the more severely affected. A wound score was computed as the sum of the five individual scores for each clinical parameter, with the total score ranging from 0 to 10. To be enrolled the animal had to have at least one individual clinical parameter measure of 2 and a total wound score of ≥ 4. When scoring discharge from a wound or abscess, the veterinarian was instructed to open the abscess prior to scoring.

Cats that did not have a positive Day 1 (pre-treatment) bacterial culture for *Pasteurella multocida*, *Actinomyces odontolyticus*, *Actinomyces viscosus*, *Escherichia coli*, *Enterococcus* spp., beta-hemolytic *Streptococcus* spp., *Staphylococcus aureus*, *Staphylococcus pseudintermedius*, *Staphylococcus felis*, or other bacteria considered relevant to the disease were excluded.

The wound scoring system described above was used to evaluate the wound or abscess on Day 1 prior to treatment (qualifying score), Day 3/4, Day 8 ± 1, and Day 15 ± 2. Each of the five clinical parameters were scored separately and assigned a classification score of zero, 1, or 2. The individual scores were then added together for a

total score, with a maximum score of 10 and a minimum score of zero.

4) Drug Administration: Cats in the VERAFLOX group were given a target dose of 3.4 mg of VERAFLOX per lb (7.5 mg/kg) of bodyweight. Cats in the placebo group were given a target dose of 0.3 mL per kg bodyweight of placebo. Cats in both groups were treated once daily for 7 days. Cats were fed free choice or within 2 hours of dosing.

5) Measurements and Observations: Bacterial cultures and cytology samples were obtained from wounds and abscesses on Day 1.

   A complete blood count (CBC), serum chemistry profile, and urinalysis were collected prior to treatment (Day 1) and at the post-treatment (Day 8 ± 1) visit. If a cat was determined to be a treatment failure at any visit prior to Day 8 ± 1, samples for a CBC, serum chemistry profile, and urinalysis were collected and FeLV/FIV testing was performed on serum collected during the Day 1 visit.

   Wound/abscess scoring was conducted on Day 1 for study inclusion and repeated on Day 3 (or 4), on Day 8 (±1 day), and on Day 15 (±2 days) if applicable. To allow for adequate wound scoring, warm compressing of wounds and flushing of drains (after Day 1) were prohibited treatments.

   The case was considered a treatment failure and was rescued if there was purulent discharge at any time after Day 1 or if there was no improvement on the Day 3 (or 4) Wound Score. Cats could also be rescued from the study due to worsening of general condition and were considered treatment failures. Cats that had a Wound Score greater than zero with no purulent discharge on Day 8 (±1 day) but scored less than their Day 1 Score were considered improved. All cats that were a treatment failure or improved on Day 8 were evaluated via owner contact on Day 15 (±2 days) for adverse events occurring after last treatment. Cats that had a Wound Score of zero on Day 8 were reevaluated on Day 15 to check for relapse.

6) Statistical Analysis: The primary measure of effectiveness was based on Study Cure, defined as a Day 8 ± 1 "Cured" classification with no relapse on the Day 15 ± 2 recheck. A relapse was defined as a Wound Score greater than zero. All other wound classifications were considered non-cures. Classifications are outlined in Table 4 below.

The non-cure classifications included:

i. Cats that were "Treatment Failures" on Day 3/4.

ii. Cats that were "Treatment Failures" or "Improved" on Day 8.

iii. Cats that were "Cures" on Day 8 ± 1 but relapsed on Day 15 ± 2. A relapse was a Wound Score greater than zero.

Table 4. Classification of treatment effect.

Exam Date	Wound Score Parameters	Case Classification	Primary Measure of Effectiveness: Cure/Non-Cure
Day 3/4	Wound score =0	Cured	Final classification made at Day 8 or 15
Day 3/4	Wound score > 0 but less than Day 1 score	Improved	Final classification made at Day 8 or 15.
Day 3/4	Wound score ≥ Day 1 score and/or purulent discharge present	Treatment Failure	Non-cure
Day 8 ± 1	Wound score =0	Cured	Final classification made at Day 15.
Day 8 ± 1	Wound score > 0 but less than Day 1 score	Improved	Non-cure
Day 8 ± 1	Wound score ≥ Day 1 score and/or purulent discharge present	Treatment Failure	Non-cure
Day 15*	Wound score > 0	Relapse	Non-cure
Day 15*	Wound score = 0	No relapse	Cure

*Cats that had a Wound Score of zero on Day 8 were reevaluated on Day 15 to check for relapse.

e. Results: Two hundred eighty-two (282) cats were enrolled in this study: 190 cats in the VERAFLOX Oral Suspension group and 92 in the placebo (vehicle without active ingredients) group. One hundred cats were excluded from the effectiveness analysis. The most common reason for exclusion was failure to meet the microbiological enrollment criteria. Other reasons for exclusion included insufficient number of evaluable cases from a site and protocol deviations.

1) Primary measure of effectiveness: The effectiveness analysis was based on 182 cats. The database included 66 placebo-treated cats and 116 VERAFLOX-treated cats. As demonstrated in Table 5, the statistical evaluation of the primary effectiveness endpoint (Study Cures) showed that VERAFLOX was different from the placebo with 73.4% study cures versus 38.9% placebo study cures. Study cure

rates were determined approximately 15 days after initiation of therapy.

Table 5. Summary of the statistical analysis.*

Treatment Group	Percent Cures
VERAFLOX N= 116	73.4 %
Placebo N= 66	38.9%

**P-value= 0.0053*

2) Secondary measure of effectiveness: A secondary measure of effectiveness was the Veterinarian's Assessment. Veterinarians assessed the success of treatment taking into account the attitude, rectal temperature, and Wound Score of the cat. As shown in Table 6, there was a statistically significant difference between groups regardless of study day.

Table 6. Summary of Veterinarian's Assessment*

Treatment Group	Percent Success in Managing Infection: Day 3 (or 4)	Percent Success in Managing Infection: Day 8 (± 1)
VERAFLOX	88.7	98.6
Placebo	60.6	86.9

** P-value=0.0065*

3) Microbiology results: Bacterial pathogens were identified to the species level when possible. Minimum inhibitory concentration (MIC) testing to pradofloxacin was conducted on Day 1 pathogens according to applicable Clinical and Laboratory Standards Institute (CLSI) standards. The MICs of pathogens with a minimum of 10 evaluable pradofloxacin treated cases classified as a Study Cure are shown in Table 7. Only two isolates from two pradofloxacin treatment failure cases had elevated pradofloxacin MICs (non-hemolytic *Staph. aureus*- MIC = 2µg/mL; *E. coli*- MIC = 4µg/mL).

Table 7. Activity of VERAFLOX against pathogens isolated from treated cats.

Pathogen	Treatment Outcome	Number of Isolates	Sample Collection (Relative to Treatment)	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Pasteurella multocida	Success	40	Pre-Treatment	0.008	0.015	≤ 0.004 - 0.03
	Failure	11	Pre-Treatment	0.008	0.008	≤ 0.004 - 0.015
Streptococcus canis	Success	13	Pre-Treatment	0.12	0.12	0.03 - 0.25
	Failure	2	Pre-Treatment	n/a	n/a	0.06 - 0.12
Staphylococcus aureus	Success	10	Pre-Treatment	0.12	0.12	0.015 - 0.12
	Failure	0	n/a	n/a	n/a	n/a
Staphylococcus felis	Success	13	Pre-Treatment	0.03	0.06	0.03 - 0.12
	Failure	1	Pre-Treatment	n/a	n/a	0.06
Staphylococcus pseudintermedius	Success	10	Pre-Treatment	0.06	0.06	0.03 - 0.06
	Failure	1	Pre-Treatment	n/a	n/a	0.03

4) Adverse Reactions: Two hundred and eighty two (282) cats were included in the field safety population. Adverse events are summarized in Table 8.

Table 8. Adverse reactions in the treated and placebo groups.*

Adverse Reaction	VERAFLOX (N= 190)	Vehicle (N= 92)
Diarrhea / loose stools	7	2
Leukocytosis with neutrophilia	4	6
Elevated CPK levels	4	4
Sneezing	4	1
Hematuria	2	2
Hypersalivation	2	1
Pruritus	2	0
Inappetence	1	3
Lethargy	1	2
Cardiac murmur	1	1
Reclusive behavior	1	1
Vomiting	1	1
Bacteriuria	1	0
Lymphadenopathy	1	0
Polydipsia	1	0
Upper respiratory infection	1	0
Fever	0	4
Anemia	0	1
Conjunctivitis	0	1
Constipation	0	1
Dilute urine	0	1
Dyspnea	0	1
Eosinophilia	0	1
Nasal discharge	0	1

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

There was one serious adverse reaction in the placebo group: dyspnea secondary to congestive heart failure. Two cats (one placebo, one VERAFLOX) had heart murmurs ausculted on Day 15 ± 1 which had not been previously noted during the study. The cat treated with VERAFLOX had a heart murmur noted prior to study enrollment by a different veterinarian.

5) Clinical Pathology: Albumin, urea nitrogen (BUN), calcium, and cholesterol showed statistically significant differences between groups. All least square means values for the statistically significant chemistry parameters were within the laboratory reference ranges and were not considered

clinically relevant. Hematology results revealed statistically significant differences between groups for lymphocytes, absolute neutrophils, percent neutrophils and WBCs, with the VERAFLOX group values slightly lower for all but the lymphocytes. Decreases in neutrophils and WBCs were expected with the resolution of infection. Three feline leukemia positive cats treated with VERAFLOX were noted to have leukopenia and/or neutropenia on Day 8.

f. Conclusions: VERAFLOX Oral Suspension administered at 7.5 mg/kg (3.4 mg/lb) once daily for 7 days was safe and effective in the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and *Staphylococcus pseudintermedius*.

III. TARGET ANIMAL SAFETY:

A. Target Animal Safety Study of VERAFLOX (Pradofloxacin 25 mg/mL) Oral Suspension in 12-week-old Kittens; Study No. 151.383/1112-007.

1. Type of Study: Laboratory safety study

2. Study Director: Edwin I. Goldenthal, PhD, ATS
Mattawan, MI

3. Purpose : To evaluate the safety of the administration of VERAFLOX Oral Suspension to 12-week-old kittens at doses of 0, 1, 3, or 5 times the maximum label dose (7.9 mg/kg) once daily for 21 consecutive days.

4. General Design:

a. Test Animals: Twenty-two male and 22 female domestic short hair kittens. Kittens were 80 to 83 days old at the start of dosing and weighed between 1.04 kg and 1.63 kg.

b. Dosage Form:
- Test Article- Pradofloxacin 25 mg/mL oral solution
- Control Article- Distilled water

c. Route of Administration: Orally via a 1 mL syringe

d. Control and Treatment Groups: The negative control (distilled water) and test substance were administered, according to treatment group as shown in Table 9, once daily for 21 consecutive days. Cats in Groups 1 through 4 were necropsied immediately following the 21-day treatment regimen, while cats in Groups 5 and 6 were maintained for an additional 45 days. During the 45 day period, cats in Groups 5

and 6 were not administered pradofloxacin, and hematology samples were collected at scheduled intervals.

Table 9. Control and treatment groups.

Treatment Group	Dose	Number and Gender of Animals
1	0X (distilled water)	4 male, 4 female
2	1X (7.9 mg/kg)	4 male, 4 female
3	3X (23.7 mg/kg)	4 male, 4 female
4	5X (39.5 mg/kg)	4 male, 4 female
5	0X–recovery (distilled water)	3 male, 3 female
6	5X–recovery (39.5 mg/kg)	3 male, 3 female

e. Variables Measured: Cage side observations, clinical observations, body weight, food consumption, ophthalmologic examinations, visual tracking, veterinary physical examinations, electrocardiographic and echocardiographic examinations, hematology, coagulation parameters, clinical chemistry, urinalysis, serum pradofloxacin levels, bone marrow cytology, gross necropsy, and histopathologic examinations.

f. Statistical Analysis: Body weights, food consumption, numeric ophthalmic and continuous clinical pathology, and urinalysis variables were analyzed using a repeated measures analysis of covariance using fixed effects of treatment, sex, day and all interactions. For each variable, pre-treatment measurements were used as a covariate. Mean contrasts were performed to follow up on significant fixed effects. Bone marrow smear variables were analyzed using an analysis of variance with treatment, sex and the interaction as fixed effects. All tests were conducted at the 0.10 level of significance.

5. Results: All kittens survived to study termination.

a. Hematology, Clinical Chemistry, and Bone Marrow Evaluations: There were decreases in leukocytes, neutrophils, and lymphocytes for the overall statistical comparisons involving the 3x and 5x groups and the control group. Individual leukocyte and lymphocyte values for all treated animals remained within the reference range. One 3X cat and three 5X cats had absolute neutrophil counts below the

reference range during the treatment period. On postmortem bone marrow cytology, the 3X cat and two of the three 5X cats had decreased myeloid:erythroid (M:E) ratios, supportive of bone marrow suppression, specifically myeloid hypoplasia. The 3X cat was neutropenic on the last day of the study prior to scheduled euthanasia on Day 21, while absolute neutrophil values for the three 5X cats returned to normal either during treatment or during the recovery period after the cessation of treatment. In addition, one of the three 5X cats had a decreased total red blood cell count on Day 15.

b. Adverse Clinical Effects: The most frequent abnormal finding was soft feces. While this observation occurred in both treated and control groups, it was seen more frequently in the 3X and 5X cats. The most severely affected animal was a 5X male who was noted to have soft stools on Days 3, 6 to 11, 13, 16 to 17, and 20 to 21. Hypersalivation was noted in one 5X cat.

c. Echocardiographic Evaluations: Reductions in left ventricular performance were noted in one 3X male cat and one 5X male cat. The clinical significance of these findings is unknown.

d. Histopathology: Minimal degeneration/necrosis of the epiphyseal cartilage was noted in the femur of one 3X male kitten. This is considered to be an incidental lesion.

e. Pharmacokinetics: Blood samples were collected for pradofloxacin concentrations at hours 1 (approximate Cmax), 10 (during elimination phase), and 24 (trough concentrations) post treatment on Days 1, 11, and 21. The Cmax values of the 1X and 3X treatment groups increased in an approximate dose-proportional manner, with a less than dose-proportional increase in drug exposure observed in the 5X group (2.8X exposure on Day 1 and 4.46X exposure on Day 21). The change in cell count from Day -6 to Day 21 for neutrophils, total leukocytes, and lymphocytes was analyzed among the four treatment groups to determine if there were any trends. Compared to the 0X group, there was a trend towards a decrease in neutrophil count as a function of day regardless of dose, but there was no correlation between Day 21/Day -6 neutrophil ratio and Cmax on Day 21. Despite the trend of a decrease in neutrophils, the cell count remained within the normal reference range for all except 6 animals.

6. Conclusions: All kittens survived to the end of the 21 day study. Neutropenia was seen in one 3X cat and three 5X cats, and bone marrow cytology was suggestive of bone marrow suppression in the 3X cat and two of the three 5X cats. An adequate safety margin was demonstrated in this study to support the use of pradofloxacin 2.5% oral suspension at 7.5 mg/kg for the duration of 7 days.

B. Target Animal Safety Study: Pilot Safety Study of VERAFLOX 2.5% (Pradofloxacin) Oral Suspension in 12 and 16-week-old Kittens; Study No. 152.134.

1. Type of Study: Laboratory study

2. Study Director: Edwin I. Goldenthal, PhD, ATS
Mattawan, MI

3. Purpose: To evaluate the safety of pradofloxacin oral solution in healthy 12 and 16 week old kittens.

4. General Design:

a. Test Animals: Domestic shorthair kittens, ages 70 to 71 days and 97 to 99 days at the time of enrollment.

b. Dosage Form:

(1) Test Article - Pradofloxacin 25 mg/mL oral solution

(2) Control Article - Distilled water

c. Route of Administration: Oral gavage

d. Control and Treatment Groups: The negative control (distilled water) and test substance were administered, according to treatment group as shown in Table 10, once daily for 21 consecutive days. The pradofloxacin dose was 39.5 mg/kg/day, 5X the maximum label dose. The dose volume for all groups was 1.58 mL/kg/day, with individual doses based on the most recent body weights.

Table 10. Control and treatment groups.

Treatment Group	Dose	Number and Gender of Animals
1	0X (distilled water)	2 male, 1 female 12 weeks old
2	5X (39.5 mg/kg)	4 male, 4 female 12 weeks old
3	0X (distilled water)	1 male, 2 female 16 weeks old
4	5X (39.5 mg/kg)	4 male, 4 female 16 weeks old

e. Variables Measured: Cage-side observations, body temperature, body weight, food consumption, ophthalmologic examinations, veterinary physical examinations, hematology, clinical chemistry, *in vivo* bone marrow cytology, gross necropsy, and histopathology.

5. Results: All kittens survived to study termination.

a. Hematology: Among 12 week old kittens, the 5X group demonstrated statistically significant decreases compared to the controls in the following values: absolute WBC count, the absolute neutrophil count, and in the absolute lymphocyte counts.

Among 16 week old kittens, statistically significant decreases were noted between the control and 5X cats in the segmented neutrophil and basophil counts. The reductions in peripheral white cell, neutrophil, lymphocyte, monocyte, and basophil counts are likely a treatment-related effect. Three 5X cats and one control cat had decreased platelet levels on manual count on Day 14.

b. *In vivo* Bone Marrow Cytology: Bone marrow aspirates were obtained to further investigate neutropenia and thrombocytopenia seen in three 5X cats. Results demonstrated decreased myeloid:erythroid (M:E) ratios, consistent with myelosuppression.

c. Adverse Clinical Effects: Soft feces and lacrimation were seen in both the control and treated groups, and vomiting was seen in the treated group. Ataxia was noted twice in one 5X kitten. This cat also exhibited neutropenia, thrombocytopenia, and a decreased myeloid:erythroid ratio.

d. Physical Examination: On the Day 6 veterinary examination, one 5X kitten was noted to have soft stools and mild bilateral lacrimation.

e. Histopathology: One 16 week old 5X male had a focus of trabecular hyperostosis in the humeral epiphysis in a section of the left shoulder. The relationship to treatment is unknown.

6. Conclusions: Safety concerns identified in this study include neutropenia, thrombocytopenia, decreased M:E ratios, vomiting, soft feces, and ataxia in cats administered pradofloxacin. This study supports the safe use of VERAFLOX Oral Suspension at 7.5 mg/kg for the duration of 7 days.

C. Ocular Safety Study: Subacute Oral Toxicity (ERG) Study in Cats; Study No. T3075650.

1. Type of Study: Feline ocular safety study, 23 days

2. Study Director: Dr. Frank Langewische, Wuppertal, Germany

3. Purpose: The objective of the study was to evaluate any ocular effects associated with repeated exposure to pradofloxacin in adult cats after oral administration by capsule.

4. General Design:

a. Test Animals: A total of 32 healthy, adult cats (16 male and 16 female) were enrolled in the study. The cats were 1-2 years of age at time of enrollment.

b. Dosage Form:

Test Article - Due to the large volume of liquid necessary to administer 30 mg/kg/day and 50 mg/kg/day doses, the study was performed using active ingredient (pradofloxacin) in capsules. In a separate relative bioavailability study, the rate and extent of pradofloxacin exposure resulting from the oral administration of the capsule formulation compared to the 2.5% oral suspension were shown to be comparable. Therefore, it was determined that the results obtained from this study using the capsule formulation can be used to support the ocular safety of the 2.5% oral suspension when administered at 7.5 mg/kg orally once daily for seven days.

Control Groups:
1. Untreated Control, nothing administered orally.
2. Active comparator group, 30 mg/kg enrofloxacin.

c. Dosage Used:

Table 11. Dosing groups.

Dose (mg/kg/day)	Number and Sex of Animals
0 mg/kg/day (untreated control group)	4 males, 4 females
30 mg/kg pradofloxacin group, 3.8X	5 males, 5 females
50 mg/kg pradofloxacin group, 6.3X	5 males, 5 females
30 mg/kg enrofloxacin (active comparator)	2 males, 2 females

d. Route of Administration: Oral

e. Study Duration: Twenty-three consecutive days

f. Pertinent Measurements/Observation: General health status was observed each day. Hematology and clinical chemistry samples were collected pre-treatment and at the end of the study. Pre-treatment and weekly ocular assessments included: electroretinography (ERG), fundic examinations via optical coherence tomography, and ophthalmic examinations. Body weights were recorded weekly and gross necropsy was performed on each cat at the end of the study. The eyes and optic nerves were evaluated for gross pathology and histopathologic changes (light and electron microscopy was performed on all retinas).

5. Results:

a. Observations: Vomiting occurred throughout the study in 18 of the 20 pradofloxacin-treated cats. Six pradofloxacin-treated cats also showed hypersalivation. Two pradofloxacin-treated cats had diarrhea during the study. Some pradofloxacin-treated cats also showed mild decreases in weight.

b. Laboratory findings: A dose-dependent decrease in white blood cell counts was observed in the pradofloxacin-treated cats.

c. Ocular findings: There were no abnormal function findings (rod or cone) on ERG evaluations in the pradofloxacin groups. No abnormalities were found during ophthalmic examinations in the pradofloxacin groups. No abnormal changes in retinal thickness, and volume and width of the optic disc were observed in the pradofloxacin groups. No gross pathology or abnormal histopathology was noted in the pradofloxacin-treated cats. One cat receiving 30 mg/kg/day of pradofloxacin exhibited minimal photoreceptor degeneration on light and electron microscopy of a type that differed from enrofloxacin-treated cats (comparator used in this study); the effects of pradofloxacin on these retinal changes is unknown.

6. Conclusion: Cats receiving 50 mg/kg/day of pradofloxacin showed mild weight loss. Cats receiving 30 and 50 mg/kg/day of pradofloxacin exhibited vomiting throughout the study. Reduced white blood cell counts were noted in the pradofloxacin-treated cats. No ocular side effects were noted during any of the ocular assessments in the pradofloxacin-treated cats. Therefore, ocular toxicity was not observed during this study in young, adult cats treated orally with 30 mg/kg/day or 50 mg/kg/day of pradofloxacin for 23 consecutive days.

D. Pilot Oral Toxicity Study: A Pilot Subacute Oral Toxicity Study in Cats; Study # 32872.

In a separate, 25 day pilot safety study, all cats administered pradofloxacin (four cats, 50 mg/kg/day pradofloxacin) exhibited vomiting and hypersalivation. One of the cats administered pradofloxacin also exhibited fluoroquinolone-induced neurologic signs (decreased mobility, staggering and vocalization) on Day 5 of the study.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in cats, 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 VERAFLOX Oral Suspension:

Human Warnings:
Not for human use. Keep out of reach of children.
Individuals with a history of quinolone hypersensitivity should avoid this product. Avoid contact with eyes and skin. In case of ocular contact, immediately flush eyes with copious amounts of water. In case of dermal contact, wash skin with soap and water immediately for at least 20 seconds. Consult a physician if irritation persists following ocular or dermal exposure, or in case of accidental ingestion.

In humans, there is a risk of photosensitization within a few hours after exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. Do not eat, drink or smoke while handling this product.

It is recommended that used syringes be kept out of reach of children and disposed of properly.

The Material Safety Data Sheet (MSDS) provides additional occupational safety information.

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 VERAFLOX Oral Suspension, when used according to the label, is safe and effective for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and *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 monitor the safe use of the product, including treatment of any adverse reactions.

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 the 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.