Date of Approval: May 30, 1990

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140441

Baytril Antibacterial Tablets

Enrofloxacin

Cats

This Supplemental Application amends the NADA to provide for the use of Baytril Tablets in cats. Baytril Tablets are currently approved for dogs, NADA 140-441, 54 FR 3444 (January 24, 1989).

Sponsored by:

MOBAY Corporation, Animal Health Division

The format of this FOI Summary document has been modified from its original form to conform to Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.

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I. General Information

NADA Number: 140-441

Sponsor: MOBAY Corporation, Animal Health Division
P.O. Box 390 Shawnee Mission, KS 66201

Generic Name: Enrofloxacin

Trade Name: Baytril Antibacterial Tablets

Marketing Status: Rx

Effect of Supplement: This Supplemental Application amends the NADA to provide for the use of Baytril Tablets in cats. Baytril Tablets are currently approved for dogs, NADA 140-441, 54 FR 3444 (January 24, 1989).

II. Indications for Use

A. Dogs

Baytril® (brand of enrofloxacin) Antibacterial Tablets are indicated for the treatment of the following bacterial infections:

Dermal infections (wounds and abscesses) caused by susceptiblestrains of Escherichia coli, Klebsiella pneumoniae*, Proteus mirabilis and Staphylococcus aureus.

Respiratory infections (pneumonia, tonsillitis, rhinitis) caused by susceptible strains of Escherichia coli and Staphylococcus aureus.

Urinary cystitis caused by susceptible strains of Escherichia coli, Proteus mirabilis and Staphylococcus aureus.

*Klebsiella has been recognized as a significant pathogen associated with nosocomial infections , in dogs.[1,2]

B. Cats

Baytri1® (brand of enrofloxacin) Antibacterial Tablets are indicated for the treatment of the following bacterial infections:

Dermal infections (wounds and abscesses)caused by susceptible strains of Pasteurella multocida, Staphylococcus aureus and Staphylococcus epidermidis.

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[1] Glickman, l.T. Veterinary Nosocomial (Hospital-Acquired)Klebsiella Infections. JAVMA, V.l79, No. 12, Dec. 15, 1981, 1389-1392.
[2] Kaufman, J. Nosocomial Infections: K lebsiella. The Compendium on Continuing Education, V.6, No. 4, April 1984, 303-310.

III. Dosage Form(s), Route(s} of Administration and Recommended Dosage(s):

The optimum dose of Baytril® (brand of enrofloxacin} Tablets in dogs and cats has been established at 2.5 mg/kg (1.13 mg/lb} of body weight administered twice daily (every 12 hours}. Baytril Tablets should be given twice daily for 2-3 days beyond the cessation of clinical signs to a maximum of 10 days. If no improvement is seen within 5 days, the diagnosis should be re-evaluated and a different course of therapy considered.

Dosage Chart

Animal Weight	BAYRIL Tablets*
2.3 kg (5 lb.)	1 x 5.7 mg tablet twice daily
9.1 kg (20 lb.)	1 x 22.7 mg tablet twice daily
27.2 kg (60 lb.)	1 x 68.0 mg tablet twice daily

*The 5.7 and 22.7 mg tablets are single scored and the 68 mg tablet is double scored for accurate dosing.

IV. Effectiveness:

A. Pivotal Studies

1. Cross-reference to existing FOI Summary for Baytril® (brand of enrofloxacin} Antibacterial Tablets, NADA 140-441, 54 FR 3444 (January 24, 1989).

   The original FOI Summary contains the details of dose titration and dose confirmation morlel studies which established the dose and efficacy for the tablet formulation in dogs. In addition, pharmacokinetic and body fluid/tissue level studies profile the distribution of enrofloxacin in dogs, while in vitro microbiological studies demonstrate the drug's activity against a variety of bacterial pathogens. Finally, both pivotal and corroborative clinical evaluations were conducted to confirm the antibacterial activity of the enrofloxacin tablet formulation in dogs.

2. Bioequivalency Evaluation of Enrofloxacin Serum Levels in Dogs vs. Cats - Single 2.5 mg/kg (1.13 mg/lb)Oral Dose - H. D. McCurdy and D. D. Copeland, Shawnee Mission, KS.

   The purpose of this trial, conducted in accordance with the July 1985 Bioequivalence Guideline, was to compare enrofloxacin serum levels in cats with those in dogs when each received the recommended dose of 2.5 mg/kg (1.13 mg/lb) body weight (b.w.) as a single oral administration using the Baytril Tablet formulation approved for dogs. The study was conducted in two separate trials. Each trial included 12 dogs and 12 cats, for a total of 24 dogs (positive control group)and 24 cats(test group). In one tria1 two cats were omitted from analysis because one lost its dose and the other cat was mistaken for the first and not sampled. Therefore, the pooled data from the two trials included 24 dogs and 22 cats. All animals were acclimated to their surroundings and were in good condition prior to being used in this study. Blood samples were collected at regular intervals beginning prior to dosing and continuing for 24 hours after dosing. Serum samples were submitted to an independent laboratory for microbiological assay of enrofloxacin levels. .The samples were not identified to the laboratory other than by animal number and bleeding interval; i.e. the study was blinded. These data were compiled and

submitted to a veterinary pharmacokineticist for statistical analysis. Statistical comparisons of means for significant differences were performed using 2-ta1led tests (Fig 1 and Table 1}. The cats maintained the serum levels longer producing an area-under-the-curve (AUC) that was larger than for dogs (P<O.OS). This was presumably due to a different rate of metabolism 1n the cat. With respect to the AUC, the study did not meet the Bioequivalence Guideline in the classical sense. However, this is not medically significant since an adequate safety margin has been demonstrated in the cat (Sect V. Animal Safety). The peak serum level (C max)and the time to reach the peak concentration (T max)were not different (P>O.OS). C max was considered important, since a lower peak concentration would reduce the effectiveness of the antibacterial. Based on the bioequivalence of the C max and T max and an adequate safety margin for enrofloxacin in cats, it was determined that 2.5 mg/kg, the dose approved for dogs, is the optimal dose for cats. No adverse effects were observed.

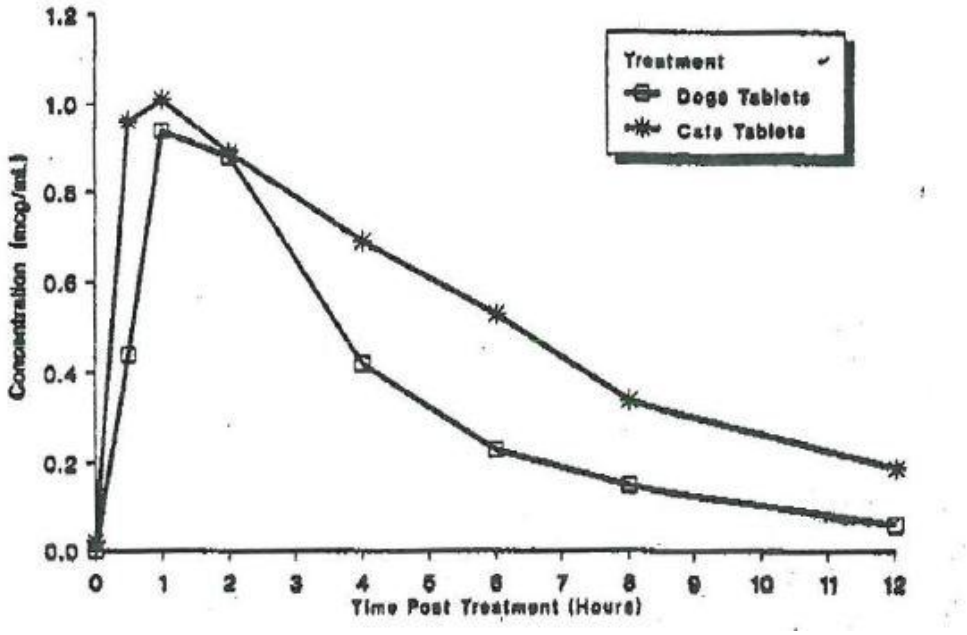

Figure 1- Enrofloxacin Bioavailabillty Study

Table 1 Canine/Feline Bioequivalency

	Dogs	Cats
Animals	24	22
Peak (mcg/mL)	1.10	1.21
SEM*	0.06	0.07
Time to Peak (hrs)	1.16	1.64
SEM	0.1	0.36
AUC+	4.4	8.1
SEM	0.4	0.6

* Standard error of the mean + Area Under the Curve

3. Enrofloxacin Tablets Clinical Trial in Cats

The investigators (listed below)participated in a

well-controlled, blinded, clinical trial from October 1988 through March 1989.

1. Dr. K. Acre - Winter Park, FL
2. Dr. L. Becker - Concord, CA
3. Dr. s. Collier - Panama City, FL
4. Dr. s. Core - Abilene, TX
5. Dr. L. Corry - Lithonia, GA
6. Dr. P. Curasi - Winter Park, FL
7. Dr. K. Duesenberg - Panama City, FL
8. Dr. R. Gessner - Winter Park, FL
9. Dr. R. Gilger - Lithonia, GA
10. Dr. R. Heers - Tulare, CA
11. Dr. J. Kelley - Orleans, MA
12. Dr. T. Kubicka - Concord, CA
13. Dr. T. Lamp - Bellville, TX
14. Dr. B. Landenberger - Winter Park, FL
15. Dr. L. LaRoux - Panama City, FL
16. Dr. R. Mauldin - Oklahoma City, OK
17. Dr. c. Moe - Oklahoma City, OK
18. Dr. D. Peddie - Middlebury, CT
19. Dr. J. Schaeffler - Concord, CA
20. Dr. A. Sumerlin -Winter Park, FL
21. Dr. Barbara Stein, Chicago, IL
22. Dr. K. Winters - Overland Park, KS

The purpose of this field study was to compare the clinical efficacy and safety of enrofloxacin tablets in cats with Hetacin K tablets, the positive control drug. This trial was conducted according to a uniform protocol using the enrofloxacin tablet formulation currently approved for dogs.

The cats were assigned to a treatment group by body system according to an individually prepared, computer generated Randomization Schedule. The study was blinded in that the investigator was not informed of the drug being used until after all evaluations were completed. Both the test and control medications were given as tablets by oral administration at 2.5 mg/kg {1.13 mg/lb) twice daily (BID) for up to 10 days. Hetacin K® was given according to the label, one 50 mg tablet BID, also for up to 10 days.

The bacterial infections studied included dermal, dental, otic, respiratory, enteric and urinary systems in cats. Cats were selected for study based on a natural infection identified by the presence of clinical signs and a bacterial culture. Data were submitted on multiple breeds, plus mixed breeds including both sexes, ages ranging from 2 months to 17.8 years and weights from 0.2 to 8.2 kg {0.5 to 18.0 lbs.). Of the 246 cats initially assigned to a study group, 23 were omitted from any efficacy assessment because of deviations from the protocol that could be expected to influence the results including those cats that did not complete the study. Clinical evaluations were subsequently conducted on 223 cats, 111 dosed with enrofloxacin and 112 with the positive control {Table 2}. An additional 56 cats were omitted from microbiological evaluations because of incomplete culture data. The microbiological

assessment was conducted on 167 cats, 86 treated with enrofloxacin and 81 with the positive control.

Table 2 Clinical Trial Case Distribution

Body System	For Clinical Evaluation		For Microbiological Evaluation	
	Enrofloxacin	Hetacin K	Enrofloxacin	Hetacin K
Dermal	65	72	51	56
Dental	3	1	3	1
Otic	2	1	2	1
Respiratory	2	24	20	16
Enteric	6	6	6	3
Urinary	8	8	4	4
Total	111	112	86	81

Efficacy was evaluated by three methods. The infections were rated according to a uniform scoring system (i.e. O=normal through 4=most severe). All systems, except urinary tract infections, were rated according to before and after treatment scores. Urinary tract infections were assigned scores only after treatment. Comparison with the positive control was accomplished by comparing the percentage reduction in the score for each system. The second method of evaluation was the elimination of pathogens. This was done by comparing the results of the pretreatment and post-treatment cultures. Subjective evaluations for ease of administration, efficacy and safety according to established uniform definitions formed the final evaluation method. Efficacy determinations were based on medical decisions. The data, therefore, are presented as means and percentages rather than with statistical analysis.

The results from each of these evaluations are presented in tabular form. Table 3 illustrates the percentage reduction in dermal, dental, otic, respiratory and enteric scores and the percentage of urinary tract scores that were listed as improved or normal at the post-treatment evaluation. Enrofloxacin had a medically pronounced effect on lesion scores from those systems, similar to Hetacin K®.

Table 3 Clinical Score Evaluation

System	Treatment	Cases	%Reduction
Dermal	Enrofloxacin	65	91.5
	Hetacin K	72	88.5
Dental	Enrofloxacin	3	75.0
	Hetacin K	1	50.0
Otic	Enrofloxacin	2	85.7
	Hetacin K	1	100.0
Respiratory	Enrofloxacin	27	84.8
	Hetacin K	24	78.3
Enteric	Enrofloxacin	6	100.0
	Hetacin K	6	87.5
			Improved or Normal
Urinary	Enrofloxacin	8	100.0
	Hetacin K	8	87.5

Culture results, based on pathogen elimination, are presented in Table 4 by body system.

Table 4 Overall Pathogen Elimination

	Percent Eliminated (Total Isolates)	
	Enrofloxacin	Hetacin K
Dermal	98.6 (71)	93.8 (81)
Dental	40.0 (5)	100 (1)
Otic	100 (3)	100 (1)
Respiratory	84.8 (33)	84.0 (25)
Enteric	80.0 (10)	0 (3)
Urinary	100 (4)	75.0 (4)
Total	91.3 (126)	88.7 (115)

Three dermal pathogens, i.e. *Pasteurella multocida, Staphylococcus aureus* and *Staphylococcus epidermidis* were identified with the greatest frequency (Table 5). No medically significant differences in dermal isolates were identified between the test and control groups of cats, with respect to the bacterial elimination of dermal isolates of *Pasteurella multocida, Staphylococcus aureus* or *Staphylococcus epidermidis*.

Table 5 Specific Dermal Pathogen Elimination

Total Isolates	Percent Eliminated (Total Isolates)	
	Enrofloxacin	Hetacin K
P. multocida	100 (15)	100 (17)
S. aureus	100 (10)	76.9 (13)
S. epidermidis	92.3 (13)	90.9 (11)
Totals	97.4 (38)	90.2 (41)

Subjective evaluation results are presented in Table 6. There were no appreciable differences between treatments with respect to the subjective impressions.

Table 6 Subjective Evaluations

		Percent of Cases	
Parameter	Rating	Enrofloxacin	Hetacin K
Ease of Administration	Excellent to Good	96.4	100
	Fair to Poor	3.6	0.0
Efficacy	Excellent to Good	93.7	91.1
	Fair to Poor	6.3	8.9
Safety	Excellent to Good	100	100

No drug-related side effects were observed during this study with either antibacterial.

Enrofloxacin tablets were safe and effective in treating the feline infections evaluated in this study. Sufficient cases were studied to establish a label claim for dermal infections in cats caused by susceptible strains of *Pasteurella multocida, Staphylococcus aureus* and *Staphylococcus epidermidis*.

B. Corroborative Study:

Evaluation of Tissue/Body Fluid Distribution of BAY Vp 2674 (enrofloxacin)in the Cat - J. D. Craven and H. D. McCurdy, Shawnee Mission, Ks.

Twelve adult cats received a single oral dose of enrofloxacin at 2.5 mg/kg (1.13 mg/lb)body weight, the recommended dose, to study the distribution of enrofloxacin in cats. The formulation used was the one that is approved and marketed for dogs. A wide range of tissue and body fluid samples were collected at 2, 6 and 12 hours after dosing (2 males and 2 females at each time interval). The study was controlled in that blood samples were collected prior to treatment, i.e. each animal was its own control. The samples were submitted to an independent laboratory for microbiological assay of enrofloxacin levels. The results demonstrated that enrofloxacin was present in all samples tested at all intervals at levels which exceeded the minimum inhibitory concentrations for many pathogens (Table 7). With limited exceptions, the tissue/body fluid levels were similar to or exceeded the serum levels.**No adverse effects were observed.

Table 7 Tissue/Body Fluid Levels* of BAY Vp 2674
In Various Systems of the Cat

	Hours Post Medication		
	2 Hour	6 Hour	12 Hour
Fluids			
Bile	2.13	9.67	1.97
Cerebrospinal fluid	0.37	0.25	0.10
Eye fluids	0.45	1.33	0.65
Serum	0.48	0.58	0.18
Urine	12.81	31.63	26.41
Tissues			
Hematopoietic System			
Bone Marrow	1.68	0.86	0.64
Liver	1.84	1.93	0.37
Lymph node (mesenteric)	0.49	0.57	0.21
Spleen	1.33	0.79	0.52
Urogenital System			
Bladder Wall	1.16	0.86	0.64
Kidneys	1.43	1.50	0.37
Ovaries	0.78	1.01	0.56
Prostate	1.88	1.07	0.55
Testes	1.01	0.46	0.28
Uterine Wall	0.81	0.92	1.05
Gastronintestinal/ Cardiopulmonary			
Heart	0.84	0.63	0.32
Lung	0.91	0.69	0.33
Large intestine	0.94	2.20	1.10
Small intestine	2.72	2.29	0.40
Stomach	3.26	0.72	0.29
Other			
Brain	0.22	0.18	0.12
Fat	0.24	0.83	0.11

	Hours Post Medication		
	2 Hour	6 Hour	12 Hour
Feces	0.37	3.50	4.18
Mammary gland	0.36	0.33	0.30
Muscle	0.53	0.54	0.29
Skin	0.46	2.38	0.17

*Tissue levels = mcg/g
Fluid levels = mcg/mL
**See package. insert

V. Animal Safety:

A. Pivotal Studies

Pivotal safety studies for the oral use of enrofloxacin (Bay Vp 2674} in cats were conducted at Mcbay Corporation, Animal Health Division, Shawnee Mission, Kansas and at Bayer AG, Institute of Toxicology, Wuppertal, West Germany as per Good Laboratory Practice Regulations.

1. Drug Tolerance Test (Drug Tolerance Test for the Use of Bay Vp 2674 Tablets in Cats)

M. Kohlenberg and J. Shmidl of Shawnee Mission, Kansas conducted a study to define the clinical signs of toxicosis following oral administration of excessive overdoses in 4 mixed breed cats as per FDA Target Species Safety Guidelines. An additional cat served as a nontreated control. Male and female, mixed breed adult cats were given the 22.7 mg enrofloxacin tablet, in the market formulation approved for dogs, orally at daily rates of either 50 or 125 mg/kg (22.7 or 56.7 mg/lb} for up to 6 consecutive days with 2 cats per treatment group. Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histology. The study was blinded in that the laboratory conducting the clinical chemistries and the hematology values were not advised of the treatments. Also, the individual conducting the necropsies and the histopathology readings did not know which treatments were given. Table 8 presents a summary of the results. Clinical signs of toxicosis induced in the 4 treated cats were salivation, change in behavior, vomition, inappetance, depression, muscle tremors, incoordination and convulsions. The 2 cats receiving the daily treatments of 125 mg/kg expired on days 4 and 5. Trends observed in the clinical chemistry/hematology parameters for the 2 cats which expired included elevated WBC's and high neutrophil counts/low lymphocyte counts. No adverse trends occurred in the animals'which survived. No clinically significant lesions were observed at necropsy. Histologically, all tissues were within normal limits except for 2 incidences of slight/mild tubular nephrosis. Subjective evaluations made were based on medical decisions. All important observations and findings have been listed. Statistical analyses were unnecessary to support the safety conclusions drawn. The results of this study concluded that an adequate safety margin exists for the treatment of cats with enrofloxacin tablets based upon survival following the daily administration of 50 mg/kg (22.7 mg/lb} or lOX the labeled dose rate for 6 consecutive days and it defines the clinical signs associated with that treatment rate. It further describes the clinical signs and altered

clinical pathology parameters seen with a daily treatment rate of 125 mg/kg (56.7 mg/lb} or 25X the labeled dose rate prior to the cats' expiring.

Table 8 Drug Tolerance Test

Number of Animals	Treatment Rate	Results
1	Control	Normal
2	50 mg/kg (10X daily dose) for 6 days	Salivation, vomition, inappetance, depression, behavioral changes, muscle tremors, incoordination and convulsions in both
2	125 mg/kg (25X daily dose) for up to 5 days	Clinical signs as previous group and both expired on days 4 and 5

2. General Safety Evaluation in 7 to 10 Month Old Cats (General Safety Evaluation for the Use of Bay Vp 2674 Tablets in Young Cats

M. Kohlenberg of Shawnee Mission, Kansas also conducted a study in 12 male and female mixed breed cats which were 7 to 10 months of age. Four additional cats were nontreated controls. The purpose of the study was to monitor clinical signs and histopathology following use rate and elevated doses with 5.7 mg BAY Vp 2674 tablets, in the market formulation currently approved for dogs, in young cats. The enrofloxacin 5.7 mg tablets were administered orally twice daily to the 3 groups (4 animals each) at 2.5, 7.5 and 12.5 mg/kg or at a total daily dose of 5, 15 and 25 mg/kg (2.27, 6.8 and 11.34 mg/lb) for 30 consecutive days. This study was blinded in that necropsy observations and histopathology readings were made by an individual unaware of the treatments given. Also the clinical chemistry and hematology values were collected without advising laboratory personnel of the treatments. There were no clinically significant changes or biologically significant trends with regard to any of the monitored parameters, i.e., clinical signs, body weights, clinical chemistries/hematology and gross necropsy. Occasional vomition was experienced by 2 of 4 animals receiving 5 mg/kg (IX), 3 of 4 receiving 15 mg/kg (3X), 2 of 4 receiving 25 mg/kg (SX)and 1 of 4 nontreated controls. No drug-related adverse effects were reported. The histopathology report confirmed all of the soft tissue and joint samples to be within normal limits for cats. The subjective evaluations made were based on medical decisions. All important observations and findings were listed. Statistical analyses were unnecessary to support the safety conclusions drawn. This study concludes that the oral administration of enrofloxacin tablets to cats that are 7 - 10 months of age is safe at dosages of 12.5 mg/kg twice a day (25 mg/kg/day)or 5 times the labeled dose rate for up to 30 days (3 times the labeled duration).

Table 9 General Safety Evaluation in 7 to 10 Month Old Cats

Number of Animals	Treatment Rate	Results
4	Control	No clinically significant observations in any parameters (clinical signs, body weights, clinical chemistries, hematology, gross necropsy, histopathology) in any of the 4 groups of animals.
4	2.5 mg/kg twice daily for 30 days (use rate for 3X labeled duration)	
4	7.5 mg/kg twice daily for 30 days (3X use rate for 3X labeled duration)	
4	12.5 mg/kg twice daily for 30 days (5X use rate for 3X labeled duration)	

3. General Safety Evaluation in 3 to 4 Month Old Kittens (Safety Evaluation for the Use of Bay Vp 2674 Tablets in Young Kittens)

M. Kohlenberg of Shawnee Mission, Kansas further conducted a study in 12 male and female, Domestic Shorthair breed kittens which were 3 to 4 months of age. Four additional kittens were untreated control animals. The purpose of this study was to monitor the clinical signs and histopathology following administration at the use rate and elevated doses with BAY Vp 2674 tablets in kittens using the market formulation approved for dogs. Enrofloxacin tablets (5.7 mg) were administered orally to the 3 groups of 4 kittens each at a daily dose of 5, 15 and 25 mg/kg (2.27, 6.8 and 11.34 mg/lb) for 30 consecutive days. The study was blinded in that the necropsy observations and histopathology readings were made by an individual unaware of the treatments given. Also the clinical chemistry and hematology values were collected without advising the laboratory personnel of the treatments. In 15 of 16 kittens there were no clinically significant changes or biologically significant trends with regard to any of the monitored parameters, i.e. clinical signs, body weights, clinical chemistries/hematology and gross necropsy. One kitten from the high dose group became moribund on day 29 of the study after appearing clinically normal the previous day. A diagnosis of feline leukemia was concluded for this animal by the consulting pathologist based upon clinical pathology and histopathology findings. In the remaining 15 kittens, the histopathologist confirmed that all tissues were within normal limits. No lesions of the articular cartilage were observed at necropsy or histologically in this study as were observed in Study No. 4. The subjective evaluations made were based on medical decisions. All important observations and findings were listed. Statistical analyses were unnecessary to support the safety conclusions drawn.

This study concludes that the oral administration of enrofloxacin tablets to 3 - 4 month old kittens is without drug related adverse effects at daily doses of 25 mg/kg (5X the labeled dosage)for up to 30 consecutive days (3X duration).

Table 10 General Safety Evaluation in 3 to 4 Month Old Kittens

Number of Animals	Treatment Rate	Results
4	Control	No biologically significant clinical signs, or trends in clinical chemistry, hematology, gross necropsy, and histopathology parameters in any of the 4 groups of animals except for kitten noted below.
4	5 mg/kg/day for 30 days (Use rate for 3X labeled duration)	
4	15 mg/kg/day for 30 days (3X use rate for 3X labeled duration)	
4	25 mg/kg/day for 30 days (5X use rate for 3X labeled duration)	One animal expired due to feline leukemia.

4. General Safety Evaluation in 5 to 7 Month Old Kittens (General Safety Evaluation for the Use of Bay Vp 2674 Tablets in Older Kittens)

M. Kohlenberg of Shawnee Mission, Kansas conducted a study using the 5.7 mg enrofloxacin tablet in 12 male and female mixed breed kittens with an age range of 5 to 7 months. Four kittens also served as nontreated controls. The purpose of the study was to monitor clinical signs and histopathology following administration at the use rate and elevated doses with the 5.7 mg tablets of BAY Vp 2674 in 5-7 month old kittens when using the market formulation approved for dogs. Treatments for the 3 groups (4 kittens each)were given orally for 30 consecutive days at a daily rate of 5, 15 or 25 mg/kg (2.27, 6.8 or 11.34 mg/lb). This treatment schedule was equivalent to IX, 3X and SX the labeled dosage rate for 3 times the labeled duration. This study was blinded in that necropsy observations and histopathology readings were made by an individual unaware of the treatments given. Also the clinical chemistry and hematology values were collected without advising laboratory personnel of the treatments. There were no clinically significant changes or biologically significant trends with regard to any of the monitored parameters, i.e. clinical signs, body weights, clinical chemistries/hematology and gross necropsy. Findings at necropsy indicated no significant lesions of the soft tissues, however, the 2 male cats that received 25 mg/kg daily treatments had lesions of the articular cartilage. The lesions consisted of small cavitations, vesicles and/or roughened surfaces. The histopathology report confirmed lesions of the articular cartilage in the 2 cats which had shown gross lesions. Soft tissues were normal histologically for all cats as were the articular surfaces of the remaining animals. The subjective evaluations made were based on medical decisions. All important observations and findings were listed. Statistical analyses were unnecessary to support the safety conclusions drawn. The results of this study conclude that enrofloxacin treatment of 5 to 7 month old cats at daily rates of 25 mg/kg for 30 consecutive days can induce gross and microscopic lesions of some articular cartilage surfaces, but the animals were normal in all other parameters. The study further confirmed that no adverse effects occurred with daily treatments of 15 mg/kg (3 times the labeled dose rate) for 30 consecutive days (3 times the labeled duration).

Table 11 General Safety Evaluation in 5 to 7 Month Old Kittens

Number of Animals	Treatment Rate	Results
4	Control	No clinical signs, normal weight gains, no abnormal trends in clinical chemistry or hematology parameters, no gross necropsy or histopathological lesions in any of the 4 groups of animals except for 2 noted below
4	5 mg/kg/day for 30 days (Use rate for 3X labeled duration)	
4	15 mg/kg/day for 30 days (3X use rate for 3X labeled duration)	
4	25 mg/kg/day for 30 days (5X use rate for 3X labeled duration)	2 animals had lesions of the articular cartilage

5. Subacute Toxicity (Bay Vp 2674; Subacute Toxicity Study on) Cats After Oral Administration)

K. Hoffman of Wuppertal, West Germany used 15 male and female kittens (8 - 10 weeks of age)to evaluate the safety of an 0.5% oral liquid enrofloxacin formulation. This study was not performed with the tablet formulation intended for market. However, it is pertinent because it is generally recognized that a liquid formulation is more readily available than a tablet for absorption into the animal's system for the assessing of potential adverse effects. Since the entire dose of enrofloxacin in a liquid formulation is immediately available for absorption into the animal's system, instead of being meted out over time as the tablet dissolves (reference Remington's Pharmaceutical Science, 16th Edition), any adverse effects would be at least as apparent with a liquid as with a tablet. Daily oral treatments of 5, 15 and 25 mg/kg (2.27, 6.8 and 11.34 mg/lb) were given for 15 consecutive days to 3 groups of 5 animals each. An additional 5 kittens served as nontreated controls. Parameters evaluated were appearance, behavior, feed intake, body weight gain, clinical pathology, necropsy and histology. The study was blinded in that histological and clinical pathology readings were conducted without advising laboratory personnel of the treatments. Subjective evaluations were based upon medical decisions. Statistical analyses were unnecessary to support the safety conclusions drawn. No drug related adverse effects occurred in this study which was conducted under Good Laboratory Practice Regulations. The study confirmed the safety of enrofloxacin in young kittens.

The conclusion drawn is that enrofloxacin was safe in 8-10 week old kittens at doses up to 25 mg/kg for 15 consecutive days.

Table 12 Subacute Toxicity - General Safety in 8 to 10 Week Old Kittens

Number of Animals	Treatment Rate	Results
5	Control	No effects occurred upon the-parameters of appearance, behavior, feed intake, body weight gain, clinical pathology, necropsy and histology in any of the 4 groups.
5	5 mg/kg/day for 15 days (Use rate for 1.5X labeled duration)	
5	15 mg/kg/day for 15 days (3X use rate for 1.5X labeled duration)	
5	25 mg/kg/day for 15 days (5X use rate for 1.5X labeled duration)	

B. Corroborative Studies

Corroborative safety studies were conducted by Mobay Corporation, Animal Health Division, Shawnee Mission, Kansas. Additionally, clinical field trial safety studies were conducted by 22 veterinary practitioners in various geographical areas of the United States.

1. Bioequivalency Evaluation (Bioequivalency Evaluation of Enrofloxacin Serum Levels in Dogs vs Cats - Single 2.5 mg/kg Oral Dose)

   H. D. McCurdy and D. D. Copeland of Shawnee Mission, Kansas conducted a bioequivalency study in 24 adult male and female dogs (positive control group) and 24 adult male and female cats (test group) of various breeds. The enrofloxacin tablet (5.7 and 22.7 mg) formulations were administered orally at the dose of 2.5 mg/kg (1 .13 mg/lb), the label recommended dose. The formulation used v.as the one that is approved for dogs.

   Serum levels were determined prior to treatment and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post-treatment. It was concluded the dog and cat serum levels were bioequivalent and thus reference is made to the approved NADA 140-441 for additional safety considerations. Table 1 previously presented contains the results of this study. No adverse effects were observed.

2. Drug Interaction Study (Safety Evaluation for Concurrent Treatment of Cats with Bay Vp 2674 Oral Tablets and Other Commonly Used Feline Health Products)

   M. Kohlenberg of Shawnee Mission, Kansas used 12 mixed breed, male and female adult cats to demonstrate safety for concurrent treatment of enrofloxacin with an anthelmintic (febantel/praziquantel), an insecticide collar (propoxur), routine immunizations and an antibiotic (ampicillin). Enrofloxacin tablets (5.7 mg) only were administered orally at a daily rate of 10 mg/kg (4.5 mg/lb)for 10 consecutive days to 4 cats (control group). The additional 8 cats received the same enrofloxacin treatment orally plus combinations of the concurrent treatments (test group). The formulation used was that approved for dogs. Parameters monitored were clinical signs and body weights. There were no adverse effects and safety for these concurrent treatments was concluded. This study was conducted as per Good Laboratory Practice Regulations.

Table 13 Drug Interaction Study

Number of Animals	Treatment Rate	Results
4	10 mg/kg/day for 10 consecutive days (2X use rate for use duration)	No clinical signs of toxicity nor adverse effect on body weights in any of the 3 groups of animals.
4	10 mg/kg/day for 10 days plus febantel/ praziquantel (anthelmintic) plus propoxur (insecticide collar)plus standard feline immunizations	
4	10 mg/kg/day for 10 days plus ampicillin (antibiotic)	

3. Confirmation of Safety in Clinical Field Trials

Confirmation of safety for the oral use of enrofloxacin tablets in cats was achieved in clinical field trials. Twenty-two veterinary practitioners located in various geographical areas of the United States treated 124 cats with enrofloxacin. Additional information concerning the investigators, etc. may be found beginning on page 4 (section IV.A.3.) of this FOI Summary. These cats received the tablet formulation (approved for dogs) at the label recommended rate of 2.5 mg/kg (1.13 mg/lb) twice daily for up to 10 days. Breeds of cats treated were quite representative with no breed susceptibility observed. Body weight was not a factor with the weight range for the treated animals being 0.5 to 16.8 lb. Age of animals treated ranged from 8 weeks to 17 years with no age susceptibility observed. No difference in safety was observed considering sex of animals treated with 84 males and 40 females included. Enrofloxacin was administered concurrently with an anthelmintic (praziquantel), sedatives/anesthetics (xylazine, ketamine, acepromazine, barbituates, halothane, metofane}, vaccinations (rabies, feline leukemia, feline distemper}, supportives (lactated ringers, dextrose in saline)and miscellaneous therapies (prednisone, topical thiabendazole and shampoos}. No incompatibilities with other drugs were observed. No drug related side effects were observed. Veterinary practitioners rated safety for enrofloxacin treatment as excellent for 118 (95.1%) of the cases, 4 (3.2%) as good and 2 were not recorded. In conclusion, the clinical field trial safety evaluations substantiated an adequate safety margin for the oral treatment of cats with enrofloxacin if used as per the proposed label. These trials used Hetacin K tablets as the positive control.

Table 14 Safety in Clinical Field Trials

Number of Animals	Treatment Rate	Results
124	2.5 mg/kg twice daily for up to 10 days	Veterinary Practitioners rated safety as excellent for 118 (95.1%} of the cases, 4 (3.2%)as good and 2 were not recorded.

VI. Human Safety:

A. Human Food Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental NADA. The drug is labeled for use in cats, which are non-food animals.

B. Human Safety Relative to Possession, Handling and Administration

The labeling contains an adequate warning statement: "Warning: Keep Out of Reach of Children".

VII. AGENCY CONCLUSIONS:

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data consist of adequate and well controlled studies, including field investigations, demonstrating effectiveness and adequate test to demonstrate safety to the target animal.

> Dermal Infections (wounds and abscesses) caused by susceptible strains of *Pasteurella multocida, Staphlococcus aureus,* and *Staphylococcus epidermidis.*

A differential diagnosis and monitoring of a patient's progress require the professional expertise of a veterinarian. Professional diagnosis, including testing, is necessary to determine the nature of the infection, e.g. to determine whether the infection is bacterial or of some other cause. Laymen are unable to make this diagnosis for the conditions indicated for this drug because different causative organisms may produce the same signs in the animal. For proper monitoring, a veterinarian must determine the parameters to be measured, how often the measurement is to take place, and whether recovery is taking place. Therefore, the labeling for this product must contain the veterinary prescription legend.

According to the Center's supplemental approval policy (42 FR 64367) this is a Category II change. This supplement provides solely for the addition of a new species (cats) to the label for the product. The approval of this supplemental application has no adverse effect on the safety and effectiveness of the new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under Section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this new animal drug application qualifies for three years of marketing exclusivity because enrofloxacin tablets were previously approved for use in dog and new clinical or field investigations were required for this NADA to provide for use in cats.