Approval Date: December 27, 1988

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-441

B. Sponsor

Mobay Corporation
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

C. Proprietary Name

Baytril® Antibacterial Tablets

D. Product Established Name

enrofloxacin

E. Dosage Form, Route of Administration and Recommended Dosage

The optimum oral dose of Baytril® (brand of enrofloxacin) Tablets has been established at 2.5 mg/kg (1.13 mg/lb) of body weight administered twice daily. The three sizes of tablets available can be used as follows:

Weight of Dog	Baytril® (Scored)* Tablet
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.

The 2.5 mg/kg (1.13 mg/lb) dose administered twice daily should be continued for two to three days beyond the cessation of clinical signs to a maximum of ten days. If no improvement is seen within five days, the diagnosis should be reevaluated and a different course of therapy considered.

F. Indications For Use:

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

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

Respiratory infections (pneumonia, tonsilitis, 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).

1. Glickman, T.L. Veterinary Nosocomial (Hospital-Acquired) *Klebsiella* Infections. JAVMA V. 179, No. 12, Dec. 15, 1981, 1389-1392.
2. Kaufman, J. Nosocomial Infections: *Klebsiella*. The Compendium on Continuing Education, V.6, No. 4, April 1984, 303-310.

II. EFFECTIVENESS

The new animal drug application for ivermectin liquid for horses contains data demonstrating that the product is the therapeutic equivalent of EQVALAN paste. Therefore, the full spectrum of indications for use of EQVALAN paste (NADA 134-314) is applicable to EQVALAN liquid. The therapeutic equivalence demonstrated in the controlled efficacy confirmation trial and the five field trials is supported by the data from a bioavailability trial where the liquid and paste formulation were compared.

A. Pivotal Studies

1. Dose Titration in a Dermal Wound Model
   Dr. John Berg, Columbia, Mo.

   A well-controlled dermal wound model study was conducted to determine the optimum dose of enrofloxacin in dogs. Twenty seven normal adult dogs, 14 males and 13 females of mixed breeding were divided randomly into four groups: a placebo control group and three groups each treated orally for five days with enrofloxacin tablets at 0.625 mg/kg (0.28 mg/lb) BID. 2.5 mg/kg (1.13 mg/lb) BID and 5.0 mg/kg (2.27 mg/lb) BID. The formulation was the one intended for market. Two experimental wounds (neck and abdomen) were established in each dog and each wound was inoculated with a concentrated inoculum containing recent isolates of *Escherichia coli* and *Klebsiella pneumoniae*. The dogs were observed for ten days after treatment was initiated and were then necropsied. During the interval between inoculation and necropsy, the dogs were observed for clinical signs of systemic infection and were monitored for changes in body temperature, hematological change. (e.g., packed cell volume, white cell counts and differential counts) and were scored based on the severity of lesion appearance. The neck lesions were tapped at one to two day intervals and cultured for pathogens. Colony counts were made and each pathogen was given a score of 0.5 based on a uniform scoring system.

   Daily culture results provided the most useful evaluation of the dose response and the results are presented in the following table.

TABLE 1. SUMMARY OF DAILY CULTURAL RESULTS INCLUDING STATISTICAL SUMMARIES USING SCORED RESULTS

Infectious Agent	Dosage (mg/kg) (b.i.d)	Days Post-Treatment – Day 0	Days Post-Treatment – Day 1	Days Post-Treatment – Day 2	Days Post-Treatment – Day 3	Days Post-Treatment – Day 4	Days Post-Treatment – Day 6	Days Post-Treatment – Day 7	Days Post-Treatment – Day 8	Total (Days 1 to 8)	Days to clear agent (transformed)
Stat Parameter	-	X1	X2	X3	X4	X5	X6	X7	X8	X9	Y10
Escherichia coli	0	2.1 (a)	4.9 (a,b)	5.7 (a)	3.3(a)	4.4 (a)	2.6 (a)	2.0 (a,1)	0.1 (a)	23.0 (a)	2.8 (a)
Escherichia coli	0.625	2.6 (a)	5.0 (a)	3.3 (b,1)	1.1 (a,b,1)	0.4 (b,1)	0.0 (b,1)	0.0 (b,1)	0.0 (a)	9.9 (b,1)	2.1 (b,1)
Escherichia coli	2.5	3.5 (a)	2.5 (b,c,1)	1.5 (c,1)	0.5 (b,1)	0.0 (b,1)	0.0 (b,1)	0.0 (b,1)	0.0 (a)	3.9 (b,1)	2.0 (b,1)
Escherichia coli	5	1.9 (a)	2.3 (c,1)	0.4 (c,1)	0.4 (b,1)	0.0 (b,1)	0.0 (b,1)	0.0 (b,1)	0.0 (a)	3.1 (b,1)	1.7 (c,1)
Klebsiella pneumoniae	0	2.3 (a)	5.4 (a)	6.0 (a)	4.1 (a)	3.9 (a)	2.4 (a)	2.3 (a)	0.9 (a)	25.0 (a)	3.0 (a,c)
Klebsiella pneumoniae	0.625	2.6 (a)	5.6 (a)	4.7 (a,b)	3.0 (a,b)	3.0 (a,b)	2.0 (a)	1.0 (a,b)	1.0 (a)	20.3 (a,b)	3.1 (a)
Klebsiella pneumoniae	2.5	2.7 (a)	3.0 (a,1)	3.5 (b,c,1)	2.2 (a,b)	1.3 (b,1)	0.7 (a,1)	0.8 (a,b)	0.7 (a)	10.4 (b,c,1)	2.4 (b,1)
Klebsiella pneumoniae	5	2.1 (a)	3.1 (a,1)	2.1 (c,1)	1.0 (b,1)	1.0 (b,1)	0.6 (a,1)	0.3 (a,1)	0.0 (a)	8.1 (c,1)	2.6 (b,c,1)
Combined data (*K. pneumoniae* and *E. coli*)	0	4.4 (a)	10.3 (a,b)	11.7 (a)	7.4 (a)	8.3 (a)	5.0 (a)	4.3 (a)	1.0 (a)	48.0 (a)	
Combined data (*K. pneumoniae* and *E. coli*)	0.625	5.1 (a)	10.6 (a)	8.0 (b,1)	4.1 (a,b,1)	3.4 (b,1)	2.0 (b,1)	1.0 (b,1)	1.0 (a)	30.1 (b,1)	
Combined data (*K. pneumoniae* and *E. coli*)	2.5	6.2 (a)	5.5 (b,c,1)	5.0 (c,1)	2.7 (b,1)	1.3 (b,1)	0.7 (b,1)	0.8 (b,1)	0.7 (a)	16.7 (b,c,1)	
Combined data (*K. pneumoniae* and *E. coli*)	5	4.0 (a)	5.4 (c,1)	2.6 (c,1)	1.4 (b,1)	1.0 (b,1)	0.6 (b,1)	0.3 (b,1)	0.0 (a,1)	11.3 (c,1)	

Means in column with different letter in parenthesis are significantly different ($P<0.05$). Means with "1" in parenthesis are significantly different from means of 0 dosage level ($P<0.05$, one-sided).

Data are expressed as means of culture scores of animals in dosage groups for each infectious agent and for the combined data from both infectious agents. An analysis of variance on each variable or its transformed value (days to clear score) was done for the replicated experiment. A two tailed test for separation of means among all four drug levels was used and a one tailed comparison was made of mean response by dosage level to the placebo control. It was concluded from this data that 2.5 mg/kg (1.13 mg/lb) BID is the optimum dose of enrofloxacin in dogs.

No drug related adverse reactions were observed in any of the treated dogs.

2. Dose Confirmation in a Dermal Wound Model
Dr. M. L. Sharp, Vernon, Tx.

A well-controlled dermal wound model study was conducted to confirm the optimum dose of enrofloxacin in dogs. Sixteen normal adult dogs, eight male and eight female, of mixed breeding were randomly divided into two groups of eight; a placebo control group and a group treated orally with enrofloxacin tablets at 2.5 mg/kg (1.13 mg/lb) BID for five days. The formulation was the one intended for market. Two experimental wounds (neck and abdomen) were created using the model described by Dr. Berg in the dose titration study. Each wound was inoculated with recent isolates of *Escherichia coli* and *Klebsiella pneumoniae*. The dogs were all necropsied at ten days after treatment started. During the interval between inoculation and necropsy, the dogs were observed for clinical signs of systemic infection and were monitored for changes in body temperature, hematological changes (e.g. packed cell volume, white cell counts and differential counts) and were scored based on severity of lesion appearance. The neck lesions were tapped at one to two day intervals and cultured for pathogens. Colony counts were made and each pathogen was given a score of 0 to 5 based on a uniform scoring system.

There was no essential difference in clinical response between the two groups.

The average culture scores for each group are presented in the following figure:

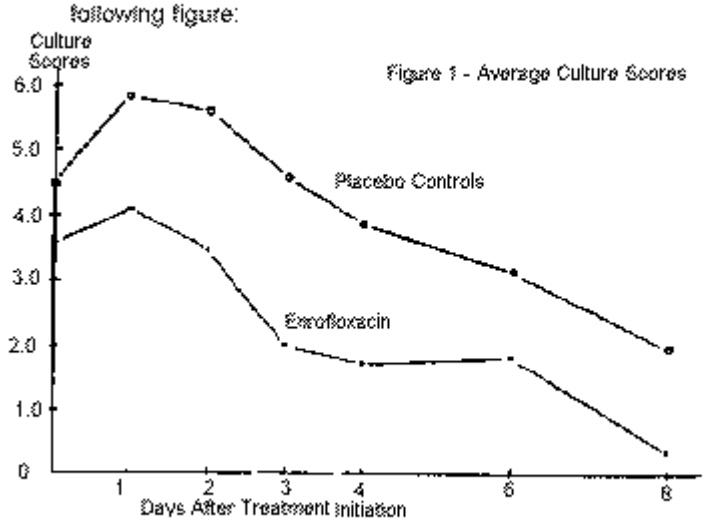


Figure 1 - Average Culture Scores

The culture counts for both organisms were lower for the enrofloxacin group when compared with the control group at Days three, four, six and eight. It was concluded from this study that enrofloxacin, at the recommended dose of 2.5 mg/kg (1.13 mg/lb) BID has a significant beneficial effect on wounds infected with *Escherichia coli* and *Klebsiella pneumoniae*. No drug related adverse effects were observed.

3. Respiratory Diesease Clinical Study
Dr. Gene Ensley, Onaga, KS

The effect of enrofloxacin against respiratory disease was evaluated in a well-controlled clinical study. Forty four puppies eight weeks of age and of various breeds were studied in a naturally occurring respiratory disease outbreak involving primarily *Staphylococcus* spp., but including isolates of *E. coli*, *Pseudomonas* spp. and *Klebsiella* spp. The infections were identified by culture of nasal swabs. The dogs were divided randomly into two groups; 23 dogs treated orally with enrofloxacin at 2.5 mg/kg (1.13 mg/lb) BID (the formulation intended for market) and 21 treated with Tribrissen tablets orally at the label recommended dose of 26.4 mg/kg (12 mg/lb) once daily. All animals were assigned to the study during a three week period. Twenty one of the enrofloxacin dogs and 19 of the Tribrissen® dogs had pretreatment cultures positive for Staphylococcus spp. The dogs were evaluated on clinical response and by culture results; i.e., by the elimination of the pathogen following up to ten days of treatment. The following scoring system was used for assigning cases and evaluating clinical response:

Score	Definition (Minimum Disease Severity)
1	Normal
2	Slight rales, respiratory congestion
3	Slight moderate rales, cough on tracheal suppression
4	Moderate rales, slight wheezing, coughing
5	Severe rales, wheezing, productive cough
6	Death of dog

Results of the enrofloxacin treated dogs were compared to the results of the positive controls in addition to a comparison to pretreatment values.

Clinical scores taken before and after treatment are shown in the following table.

Table 2. Average Clinical Scores Respiratory Infections

Group	No. Dogs	Pretreatment	Post treatment
Enrofloxacin	23	4.4	1.8
Tribrissen™	21	4.1	3.3

Overall, the treated dogs, some in poor condition (very guarded prognosis) at the start of treatment responded well with noticeable improvements within the first 24 to 48 hours following treatment initiation with the test medication. Both treatments effectively eliminated the pathogens based on pre-treatment and post treatment culture results.

This study established the efficacy of enrofloxacin for the treatment of canine respiratory disease caused by susceptible pathogens.

No drug related adverse effects were observed following enrofloxacin treatment.

4. Dose Confirmation in an Experimentally Induced Urinary Tract Infection
Dr. George E. Lees, College Station, Tx.

A well-controlled urinary tract infection model study was conducted to establish the efficacy of enrofloxacin or treating urinary tract infections. An experimentally induced bladder infection was produced in 18 normal adult dogs (nine males and nine females) of mixed breeding by irritating and inoculating the bladder with a single isolate of hemolytic *Escherichia coli*. The test animals were divided into three groups of six: a placebo control, a group treated with enrofloxacin at 2.5 mg/kg (1.13 mg/lb) BID for five days and a group treated with the same dose for ten days. Oral tablets were used and were the formulation intended for market.

The dogs were studied for 18 days with the primary parameter for evaluation being pathogen elimination. For this purpose urine samples were collected via antepubic cystocentesis after three and five days of treatment in the five day treatment group and after three, five, seven and ten days of treatment in the ten day treatment group. A urine sample was also collected four and nine days post treatment in the five day treatment group and at 4 days following treatment in the ten day tested dogs to evaluate for relapse.

The results are presented in the following table:

Table 3. Summary of Urinary Infection Results
Number of Animals with *E. Coli*

Group	No. Dogs	Dose mg/kg	Pre-Infection	Pre-Treatment	End of Treatment	Follow-up
Control	6	Placebo	0	6	6	6
5-Day	6	2.5 (1.13 mg/lb)	0	6	0	2
10-Day	6	2.5 (1.13 mg/lb)	0	6	0	1

All treated animals in both the five and ten day treatment groups became negative during treatment. Two males in the five day group and one male in the ten day group relapsed by the end of the study.

The frequency of bacteriuria in enrofloxacin treated dogs was lower than controls on the last day of treatment. Despite the relapse of infection in three treated dogs, the frequency of bacteriuria found in specimens obtained on the last day of the study from treated dogs was lower than that found in specimens from the control dogs. It was, therefore, concluded that enrofloxacin tablets are effective for the treatment of canine urinary tract infections caused by susceptible organisms.

Drug related adverse effects were not observed in any of the enrofloxacin treated dogs.

5. Clinical Field Trial

Dr. Ben Baker, Fort Smith, AK
Dr. Dennis Cloud, St. Louis, MO

Dr. Sara H. Core, Abilene, TX
Dr. Richard B. Ford, Raleigh, NC
Dr. Richard G. Heers, Tulare, CA
Dr. Mark Hutton, Wichita, KS
Dr. Ted Lamp, Bellville, TX
Dr. Richard Mauldin, Oklahoma City, OK
Dr. Nick Nail, Broken Arrow, OK
Dr. Frank Serra, Overland Park, KS

A well-controlled, blinded clinical investigation involving 10 investigators was conducted according to a uniform protocol. Tribrissen® tablets were used as a positive control. A total of 107 enrofloxacin and 78 Tribrissen® treated dogs (96 male and 89 female) of various breeds, ages (6 wks to 23 yrs) and weights were included in the study. Dogs with dermal, enteric, upper respiratory tract, lower respiratory tract or urinary tract infections were treated by severity of infection using a uniform scoring system (i.e. 0=normal through 4=most severe). The dogs within each infected body system were assigned via a randomization schedule to receive treatment with either enrofloxacin at 2.5 mg/kg (1.13 mg/lb) BID or Tribrissen at the rate of 26.4 mg/kg (12 mg/lb) SID. A pre-treatment culture sample was obtained to identify the bacterial pathogens and the dogs were then treated with the designated tablets orally for five to ten days. Upon completion of treatment the dogs were returned to the investigator to score the treatment response and to obtain a post treatment culture sample. The investigator was unaware of which drug each dog received until the case was completed.

The study was conducted over a three month period. The pertinent parameters measured were clinical response and bacteriological response (pathogen elimination).

The clinical response was measured by comparing pre treatment and post treatment clinical scores. Twelve enrofloxacin and 14 Tribrissen® cases were excluded from this assessment for the reasons given in Table 4.

Table 4. Cases Where No Evaluation of Clinical Response Could Be Made

No. of Cases	Group	Reason
3	Enrofloxacin	Concurrent therapy
5	Enrofloxacin	Examination post-treatment too late
2	Enrofloxacin	Treatment stopped due to side effects
2	Enrofloxacin	Diagnosis not covered by protocol
12		
6	Tribrissen®	Concurrent therapy
3	Tribrissen®	Examination post-treatment too late
2	Tribrissen®	Follow-up evaluation while on medication
2	Tribrissen®	Diagnosis not covered by protocol
1	Tribrissen®	Wrong dosage administered
14		

Four enrofloxacin and two Tribrissen® cases had infections involving two body systems simultaneously. Each body system was evaluated and counted

separately; therefore, a total of 99 enrofloxacin and 66 Tribrissen® cases were assessed for clinical response (Table 5).

Table 5. Pre and Post-Treatment Clinical Scores

Type of Infection	No. of Cases	Enrofloxacin – Mean Pre-treat Score	Enrofloxacin – Mean Post-treat Score	No. of Cases	Tribrissen® – Mean Pre-treat Score	Tribrissen® – Mean Post-treat Score
Dermal	46	3.2	0.8	36	3.3	0.8
Enteric	6	1.7	0	1	2.0	0
Upper Respiratory	18	3.3	0.8	9	3.0	0.7
Lower Respiratory	2	2.5	1.0	1	3.0	1.0
Cystitis	21	*	0.3	16	*	0.7
Other Urinary**	6	*	0.3	3	*	0

* cystitis was not scored on the pre-treatment examination
** urethritis, prostatitis, nephritis, vaginitis and bacteriuria

Only dermal infections, respiratory tract infections and cystitis provided sufficient data for evaluation. For dermal and respiratory tract infections, pre-treatment, post treatment, and the difference between pre and post treatment scores were analyzed. Clinically significant reductions in post treatment scores were observed. Comparisons between treatment groups were also made and evaluated. There was essentially no medically significant difference between the two treatment groups.

For cystitis, post treatment scores were compared. Clinically, there was essentially no difference between treatment groups.

Criteria for the bacteriological response were based upon the elimination of the initial pathogen from the post treatment culture or if response to therapy was such that healing precluded the availability of a culture. Animals not considered for this evaluation (in addition to those listed in Table 4) are presented in Table 6.

Table 6. Cases Where No Evaluation of Bacteriological Response Could Be Made

No. of Cases	Group	Reason
18	Enrofloxacin	No significant growth on pre-treatment culture
2	Enrofloxacin	Post-treatment culture taken too late
1	Enrofloxacin	Pre-treatment culture taken too early
1	Enrofloxacin	No post-treatment culture
14	Tribrissen®	No significant growth on pre-treatment culture
1	Tribrissen®	Pre-treatment culture taken too early
1	Tribrissen®	No post treatment culture taken

A total of 121 animals (73 enrofloxacin and 48 Tribrissen® cases) were used for this evaluation. The overall response to treatment regardless of pathogen or body system is presented in Table 7.

Table 7. Bacteriological Response

Enrofloxacin – No. of Cases	Enrofloxacin – No. of Infections Eliminated	Enrofloxacin – % Eliminated	Tribrissen® – No. of Cases	Tribrissen® – No. of Infections Eliminated	Tribrissen® – % Eliminated
73	51	70%	0	6	6

The elimination of pathogens was analyzed by comparing pre. and post-treatment bacterial culture results. From a medical standpoint, no significant difference (70% vs. 67%) in pathogen elimination was found.

The bacteriological response to treatment was also evaluated by organism. The major dermal, respiratory and urinary tract pathogens isolated from the pre-treatment culture samples were considered for this assessment. More than one pathogen was isolated from many animals resulting in a total of 91 isolates from the enrofloxacin group and 57 isolates from the Tribrissen® treated dogs.

The results are presented in Table 8.

Table 8. Bacterial Response by Organism

Pathogen	Enrofloxacin – No. of Isolates	Enrofloxacin – No. Eliminated	Tribrissen® – No. of Isolates	Tribrissen® – No. Eliminated
A. Dermal Infections				
Staphylococcus aureus	24	16 (67%)	14	7 (50%)
Staphylococcus spp.	12	9 (75%)	7	2 (29%)
Streptococcus spp.	4	3 (75%)	4	3 (75%)
Escherichia coli	5	5 (100%)	4	3 (75%)
Pseudomonas spp.	7	5 (71%)	3	3 (100%)
Proteus mirabilis	6	6 (100%)	5	5 (100%)
Klebsiella pneumoniae	0	-	1	1 (100%)
B. Respiratory Infections				
Staphylococcus aureus	1	1 (100%)	2	1 (50%)
Staphylococcus spp.	3	2 (67%)	3	3 (100%)
Streptococcus spp.	4	4 (100%)	2	1 (50%)
Escherichia coli	6	5 (83%)	2	2 (100%)
Pseudomonas spp.	3	2 (67%)	1	1 (100%)
Proteus mirabilis	1	1 (100%)	0	-
Klebsiella spp.	2	2 (100%)	0	-
B. Urinary Tract Infections				
Staphylococcus aureus	0	-	2	2 (100%)
Staphylococcus spp.	1	1 (100%)	1	1 (100%)
Streptococcus spp.	3	2 (67%)	1	1 (100%)
Escherichia coli	3	3 (100%)	2	2 (100%)
Pseudomonas spp.	1	1 (100%)	1	1 (100%)
Proteus mirabilis	4	4 (100%)	1	1 (100%)
Proteus spp.	1	1 (100%)	0	-
Klebsiella spp.	0	-	1	1 (100%)
Total	91			

Enrofloxacin was equally effective against Gram negative and Gram positive bacteria. The elimination of bacterial pathogens was evaluated by organism and there was no medically significant difference in bacterial response by organism between treatment groups (80% vs. 72%).

Vomiting was noted in three enrofloxacin treated dogs, one dog developed diarrhea and one had a decrease in appetite. Two of the vomiting cases resulted in the medication being discontinued and it was judged that the vomiting in these cases was apparently treatment related. The remaining three incidences of side effects were considered mild and probably not drug related. There were no reported side effects in the Tribrissen® treatment group.

It was concluded that under the conditions of this well controlled clinical study, enrofloxacin was safe and effective in the treatment of bacterial infections of dogs.

B. Corroborative Studies

1. Clinical Field Trial

Dr. D. Allen, Youngstown, OH
Dr. S. Cheesman, Pine Bluff, AR
Dr. S. Ensley, Onaga, KS
Dr. M. Hays, Houston, TX
Dr. R. Smithson, Nashville, TN
Dr. F. Soifer, Houston, TX
Dr. W. Yates, Raytown, MO

A clinical field study, with microbiological responses blinded, was conducted according to a uniform protocol to compare the safety and efficacy of enrofloxacin tablets and Tribrissen® tablets against specified bacterial infections of dogs. A total of 233 dogs (120 male, 113 female) including various breeds, ages (2 months to 13 years) and weights were included in the study. Dogs with bacterial infections requiring systemic treatment were rated by the severity of infection by use of a uniform scoring system (i.e. 0=normal, 4=most severe). The dogs within each infected body system were assigned to receive treatment with either enrofloxacin at 2.5 mg/kg (1.13 mg/lb) BID or Tribrissen at 26.4 mg/kg (12 mg/lb) SID with a preassigned randomization schedule. A pretreatment bacterial culture was obtained to identify the bacterial pathogens. The dogs were treated with the designated tablets orally for five to ten days.

Upon completion of treatment, the dogs were returned to the investigators to score the treatment response and to obtain a post-treatment bacterial culture.

Of the 128 enrofloxacin and 105 Tribrissen® treated cases assigned to the study, 73 enrofloxacin and 69 Tribrissen® cases were correctly completed and acceptable for efficacy evaluation.

The clinical response results are presented in the following table:

Table 9. Pre and Post-treatment Clinical Response Following Treatment

Type of Infection	Enrofloxacin – No. of Cases	Enrofloxacin – Mean Pretreat. Score	Enrofloxacin – Mean Post-treat. Score	Tribrissen® – No. of Cases	Tribrissen® – Mean Pretreat. Score	Tribrissen® – Mean Post-treat. Score
Dermal	45	3.6	0.6	43	3.2	1.1
Enteric	5	3.0	0.0	7	3.0	0.3
Upper Respiratory	6	2.7	0.0	6	2.5	0.5
Lower Respiratory	8	2.5	0.5	6	2.3	0.8
Urinary	9	*	*	7	*	*

* Urinary tract infections were not scored by severity although all of these infections improved clinically.

The results indicated no clinically significant difference between the enrofloxacin and Tribrissen® treated dogs for any of the five different infected body systems.

The bacteriological response to treatment was also evaluated. The major dermal, respiratory and urinary tract pathogens isolated from the pre-treatment culture samples were considered for this assessment. More than one pathogen was isolated from many animals resulting in a total of 86 isolates from the enrofloxacin group and 66 isolates from the Tribrissen® treated dogs.

The results are presented in Table 10.

Table 10. Bacterial Response by Organism

Pathogen	Enrofloxacin – No. of Isolates	Enrofloxacin – No. Eliminated	Tribrissen® – No. of Isolates	Tribrissen®– No. Eliminated
A. Dermal Infections				
Staphylococcus aureus	13	12 (92%)	9	7 (78%)
Staphylococcus spp.	21	16 (76%)	22	13 (59%)
Streptococcus spp.	9	6 (67%)	5	5 (100%)
Escherichia coli	4	4 (100%)	3	2 (67%)
Pseudomonas spp.	8	6 (75%)	7	6 (86%)
Proteus spp.	4	4 (100%)	3	3 (100%)
Klebsiella spp.	0	-	1	1 (100%)
B. Respiratory Infections				
Staphylococcus aureus	1	1 (100%)	2	2 (100%)
Staphylococcus spp.	3	3 (100%)	2	2 (100%)
Streptococcus spp.	7	6 (86%)	3	3 (100%)
Escherichia coli	4	4 (100%)	1	1 (100%)
Pseudomonas spp.	1	1 (100%)	1	1 (100%)
Klebsiella pneumoniae	0	-	1	1 (100%)
B. Urinary Tract Infections				
Staphylococcus spp.	1	1 (100%)	0	-
Streptococcus spp.	0	-	1	1 (100%)
Escherichia coli	4	4 (100%)	1	1 (100%)
Pseudomonas spp.	3	2 (67%)	2	1 (50%)
Proteus spp.	2	2 (100%)	1	1 (100%)
Klebsiella pneumoniae	1	1 (100%)	1	1 (100%)
Total	86	73 (85%)	66	52 (79%)

Pretreatment and post-treatment bacterial culture results were similar for both treatment groups.

Decreased appetites were noted for two dogs in the study (one treated with enrofloxacin and one treated with Tribrissen®). An additional dog, treated with enrofloxacin, vomited (twice) and had soft stools. No other adverse side effects were observed.

2. Clinical Field Trial
Dr. Waybern Yates, Raytown, MO

A clinical field study was conducted to compare the safety and efficacy of enrofloxacin tablets (the formulation to be marketed) and Tribrissen® tablets against specified bacterial infections of dogs. A total of 64 dogs (26 male, 38 female) including various breeds, ages (8 weeks to 14 years) and weights were included in the study. Dogs with bacterial infections requiring systemic treatment were rated by the severity of infection by use of a uniform scoring

system (i.e. 0=normal, 4=most severe). The dogs within each infected body system were assigned to receive treatment with either enrofloxacin at 2.5 mg/kg (1.13 mg/lb) BID or Tribrissen at 26.4 mg/kg (12 mg/lb) SID with a preassigned randomization schedule. A pretreatment bacterial culture was obtained to identify the bacterial pathogens and the dogs were then treated with the designated tablets orally for 5-10 days. Upon completion of treatment, the dogs were returned to the investigator to score the treatment response and to obtain a post-treatment bacterial culture.

Three enrofloxacin and two Tribrissen® cases were excluded from the evaluation. Both Tribrissen® cases were on medication for more than 10 days. One enrofloxacin treated dog received medication for more than 10 days, one was euthanatized at the owner's request and one was underdosed. This left 32 enrofloxacin and 27 Tribrissen® cases for evaluation.

The clinical response is presented in Table 11.

Table 11. Pre and Post-treatment Clinical Response Following Treatment

Type of Infection	Enrofloxacin – No. of Cases	Enrofloxacin – Mean Pretreat Score	Enrofloxacin – Mean Post-treat. Score	Tribrissen® – No. of Cases	Tribrissen® – Mean Pretreat. Score	Tribrissen® – Mean Post-treat. Score
Dermal	12	3.3	0.25	10	3.3	0.4
Enteric	5	3.0	0.2	3	3.3	0.0
Upper Respiratory	5	2.4	0.2	4	2.75	1.0
Lower Respiratory	4	2.75	0.25	6	2.5	0.5
Urinary	6	*	0	4	*	0

* Urinary tract infections were not scored by severity. All of the infections returned to normal following treatment.

Individual clinical scores were reduced in all enrofloxacin treated cases while these scores were not reduced in 2 Tribrissen® cases. The results indicated no clinically significant difference between the enrofloxacin and Tribrissen treated dogs for any of the 5 different infected body systems.

The bacteriological response to treatment was also evaluated. The major dermal, respiratory and urinary tract pathogens isolated from the pre-treatment culture samples were considered for this assessment. More than one pathogen was isolated from many animals resulting in a total of 23 isolates from the enrofloxacin group and 19 isolates from the Tribrissen® treated dogs.

The results are presented in Table 12.

Table 12. Bacterial Response by Organism

Pathogen	Enrofloxacin – No. of Isolates	Enrofloxacin – No. Eliminated	Tribrissen® – No. of Isolates	Tribrissen® – No. Eliminated
A. Dermal Infections				
Staphylococcus aureus	5	5 (100%)	2	2 (100%)
Staphylococcus spp.	1	1 (100%)	1	1 (100%)
Escherichia coli	1	1 (100%)	1	0 (0%)
Pseudomonas aeruginosa	1	1 (100%)	1	1 (100%)
Proteus mirabilis	1	1 (100%)	2	2 (100%)
Proteus vulgaris	2	2 (100%)	0	-
B. Respiratory Infections				
Staphylococcus aureus	1	1 (100%)	1	1 (100%)
Streptococcus spp.	5	5 (100%)	4	4 (100%)
Escherichia coli	1	1 (100%)	1	1 (100%)
Pseudomonas aeruginosa	1	1 (100%)	0	-
Klebsiella pneumoniae	1	1 (100%)	1	1 (100%)
Klebsiella spp.	0	-	1	1 (100%)
B. Urinary Tract Infections				
Staphylococcus aureus	1	1 (100%)	1	1 (100%)
Escherichia coli	2	2 (100%)	2	2 (100%)
Proteus vulgaris	0	-	1	1 (100%)
Total	23	23 (100%)	19	18 (95%)

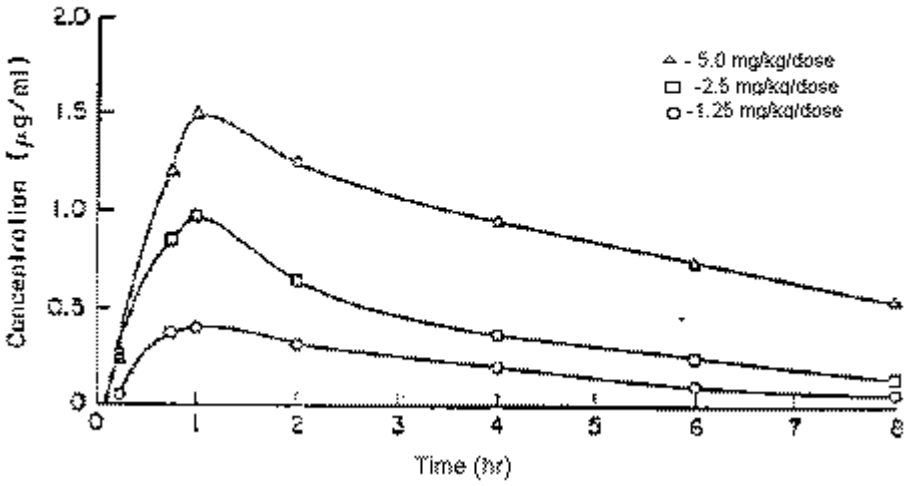
No adverse side effects were observed in any of the enrofloxacin or Tribrissen® treated dogs.

3. Pharmacokinetics in Dogs
Drs. G. V. Ling and J. D. Baggot, Davis, Ca.

Twelve healthy, conditioned, adult dogs were divided into three groups of four, each containing two males and two females. The dogs served as their own control as a pretreatment blood level of enrofloxacin was established prior to dosing. The objective of the study was to study the pharmacokinetics of enrofloxacin using three dose levels; 1.25 mg/kg (0.57 mg/lb), 2.5 mg/kg (1.13 mg/lb) and 5.0 mg/kg (2.27 mg/lb) and two routes of administration (oral and intravenous). In this trial the serum and urine levels of enrofloxacin were monitored just prior to dosing and at regular intervals after dosing. At the recommended dose of 2.5 mg/kg (1.13 mg/lb) given orally, it reached 50% of its maximum serum concentration within 15 minutes and peak concentration occurred in 1 hour. The half-life was greater than three (3) hours with both oral and intravenous doses. Approximately 80% of the orally administered dose entered the systemic circulation unchanged. The body clearance time was the same (approximately 9 ml/min/kg) at each dose rate indicating that the eliminating organs could readily remove the drug with no

indication that the eliminating mechanisms were saturated. A graph showing the mean blood levels following oral dosing at the three levels follows:

Figure 2 - Serum Concentrations of Enrofloxacin Following a Single Oral Dose



4. Antibacterial Susceptibility Study
Dr. John Berg, Columbia, Mo.

An in vitro study was conducted using 37 bacterial isolates selected based on their resistance to other antibacterials. Minimum inhibitory concentrations (MICs) for enrofloxacin were established for these isolates from dogs. Comparisons were made using Kirby-Bauer zone sizes for 12 different antibacterials. Presented below are the MIC ranges for the different pathogens studied. It was concluded from the study that enrofloxacin was highly active against all Gram-negative isolates tested and many Gram-positive isolates.

Table 13. MIC Values for Enrofloxacin Against Canine Pathogens

Organisms	Isolates	MIC Range (mcg/mL)
Bacteroides spp.	2	2
Bordetella bronchiseptica	3	0.125-0.5
Brucella canis	2	0.125-0.25
Clostridium perfringens	1	0.5
Escherichia coli	4	< or = 0.016-0.031
Klebsiella spp.	10	0.031-0.5
Proteus mirabilis	6	0.062-0.125
Pseudomonas aeruginosa	4	0.5-8
Staphylococcus spp.	5	0.125

5. Enrofloxacin Tissue/Body Fluid Distribution in the Dog
Drs. H. O. McCurdy and R. C. Stewart, Shawnee Mission, KS

Six random source dogs of similar breeding received a single oral dose of enrofloxacin at 2.5 mg/kg (1.13 mg/lb). Blood and urine samples were collected before treatment and at regular intervals following treatment and were submitted for laboratory analysis of enrofloxacin drug levels. Each dog

served as its own control. This was a preliminary trial conducted with a tablet containing 20 mg active per tablet to establish how dogs were dosed to the nearest half-tablet. Two dogs each were euthanized at 2, 4 and 8 hours after dosing and a wide range of tissues were collected to represent all major systems of the body. These were submitted for laboratory analysis for the enrofloxacin drug levels. The following table demonstrates the levels of drug achieved. It was concluded that enrofloxacin penetrates well into all tissues and body fluids measured.

Table 14. Body Fluid/Tissue Distribution of Enrofloxacin in Dogs

Substrate	Single Oral Dose = 2.5 mg/kg (1.13 mg/lb) - 2.0 Hr.	Single Oral Dose = 2.5 mg/kg (1.13 mg/lb) - 4.0 Hr.	Single Oral Dose = 2.5 mg/kg (1.13 mg/lb) - 8.0 Hr.
Body Fluids (mcg/mL)			
Whole Blood*	1.01	0.66	0.36
Plasma	0.67	0.55	0.36
Urine	43.05	33.30	55.35
Feces	1.65	4.86	9.97
Eye Fluids	0.53	0.57	0.66
Tissues (mcg/g: n=2 for each unless otherwise specified)			
Liver	3.02	2.21	1.36
Spleen	1.45	1.43	0.85
Bone Marrow	2.10	1.50**	1.22**
Lymph Node	1.32	1.36	0.91
Urogenital System			
Kidney	1.87	2.43	0.99
Bladder Wall	1.36	1.65	0.98
Testes***	1.36	1.42	1.10
Prostate***	1.36	1.36	2.20
Uterine Wall***	1.59	0.49	0.29
Gastrointestinal and Cardiopulmonary Systems			
Lung	1.34	1.49	0.82
Heart	1.88	2.25	0.78
Stomach	3.24	5.71	2.16
Small Intestine	2.10	2.82	1.11
Other Canine Tissues			
Fat Tissue	0.52	0.46	0.40
Skin	0.66	0.80	0.48
Muscle	1.62	1.58	0.77
Brain	0.25	0.42	0.24
Mammary Gland***	0.45	0.55	0.21

* Blood and plasma values based on n=6 through 2 hours; the 4 hr. with n=4 and the 8 hour samples with n=2.
** Value from 2 male samples "pooled" (1-4 hr. sample and 1-8 hr. sample).
*** One animal/test interval, all other tissues have 2 animals/group.

6. In-Vitro Susceptibility of Selected Gram-Negative and Gram-Positive Canine Urinary Bacterial Isolates to Enrofloxacin and to Seven Additional Marketed Antibacterial Agents.
Dr. G. V Ling. Davis, CA

One hundred twenty bacterial isolates representing the seven most common bacterial species in canine urinary tract infections were evaluated against seven antibacterial agents plus enrofloxacin, the test product, using microtiter dilution techniques. The range of responsiveness observed for each antibacterial to the 120 isolates is presented in the table below. The test antibacterial, enrofloxacin, had a lower overall range of in-vitro MIC values than any of the antibacterial products tested, including those commonly recommended for canine urinary tract infections. e.g. gentamicin and trimethoprim-sulpha.

Table 15. Range of Minimum Inhibitory Concentrations (MIC) to Canine Urinary Isolates

Antimicrobial	*E. coli*	*Proteus Mirabilis*	*K. pneumoniae*	*P. aeruginosa*	*Enterobacter* spp.	*Staph. Coag +*	*Strep. alpha hemol.*
Enrofloxacin	0.06-2	0.125-2	0.06-0.5	1-8	0.06-1	0.125-0.5	0.5-8
Trimeth/Sulfa*	0.125->64	0.125-2	0.125->64	2->64	0.125->64	0.125-16	0.125-64
Amoxicillin	2->256	0.5->256	32->256	64->256	0.5->256	0.125-2	0.125-32
Cefadroxil	2-128	8-64	8->256	>256	8->256	0.125-4	0.5->256
Chrloramphenicol	4->256	4-128	4->256	64->256	4->256	0.5-8	2-32
Gentamicin	0.25-8	0.25-4	0.25-16	2-8	0.125-32	0.125-8	0.5-16
Nitrofurantoin	8-64	64-128	32->128	256	16-128	0.5-8	16-256
Oxytetracycline	4->256	128-256	4->256	16-64	8->256	0.125-64	4->256
No. of isolates	30	20	20	10	10	20	10

* The MIC is the Trimethoprim only.

III. ANIMAL SAFETY

A. Pivotal Studies

The pivotal safety studies for the oral use of enrofloxacin (BAY Vp 2674) in dogs were conducted at Theracon, Inc., Topeka. Kansas and Mobay Corporation, Animal Health Division. Shawnee Mission, Kansas as per Good Laboratory Practice Regulations.

1. Drug Tolerance Test (Drug Tolerance Test for the Use of BAY Vp 2674 Tablets in Dogs).

   M. Kohlenberg and J. Shmidl of Shawnee Mission, Kansas conducted a study to define the clinical signs of toxicosis following administration of excessive overdoses in 4 dogs. Male and female, mixed breed adult dogs were given the 68 mg tablets orally at daily rates of either 50 mg/kg (22.7 mg/lb) or 125 mg/kg (56.7 mg/lb) with 2 dogs per treatment group for up to 14 consecutive days. Parameters monitored were clinical signs, body weights, body temperatures, clinical chemistries, hematology, necropsy and histology. The 2 dogs receiving 50 mg/kg (22.7 mg/lb) were observed to have infrequent episodes of vomition and one showed a loss of appetite. No other adverse effect occurred upon the parameters evaluated in these 2 dogs. The 125 mg/kg (56.7 mg/lb) treatment induced vomition, inappetence, depression and death in these 2 dogs with death occurring on Days 10 and 11. The study demonstrated the clinical signs of toxicosis (vomition, inappetence, depression, difficulty with locomotion) preceding death.

2. General Safety Evaluation in Adult Dogs (Safety Evaluation For the Use of BAY Vp 2674 Tablets in Dogs).

   M. Kohlenberg of Shawnee Mission, Kansas conducted a study in 16 adult, male and female dogs of various breeds with daily treatments at the use rate of 5 mg/kg/day (2.27 mg/lb/day). 3X use rate and 5X use rate for 30 days or 3 times the labeled duration. Four dogs were included in each treatment group plus 4 controls. The 68 mg tablet was given orally. Parameters evaluated were clinical signs, body weights, clinical chemistries, hematology, necropsy and histology. No treatment related adverse effects were observed in any of the parameters except for slight loss of appetite and depression in the dogs receiving the elevated treatments. The study concluded an adequate safety margin for the labeled treatment schedule of 5 mg/kg/day (2.27 mg/lb/day) for a maximum of 10 days.

3. Breeding Animal Study (Safety Evaluation for BAY Vp 2674 in Male Breeding Dogs).

   A. Stuke of Topeka, Kansas conducted a study in 9 male Beagle breed dogs with daily doses of the use rate of 5 mg/kg/day (2.27 mg/lb/day) and 3X the use rate for 10 consecutive days at each of 3 series of treatments. The 3 series were at 90, 45 and 14 days prior to their use for stud purposes. Each group contained 3 animals and 3 controls were included. The 68 mg tablet was given orally. The 9 males were mated to a total of 46 females with the following parameters evaluated: libido, successful pregnancies and average number of pups per litter. Libido was normal for all dogs. Eighty (80) % of the matings by the control males and those receiving the treatment rate of 5 mg/kg (2.27 mg/lb) resulted in pregnancies. An 87.5% pregnancy rate occurred with matings to males receiving the 3X treatment rate. Average number of pups born per 1itter were very comparable. The study concluded that no adverse effects occur when male dogs are treated during critical stages of reproduction.

4. General Safety Evaluation in Older Puppies (General Safety Evaluations for the Use of BAY Vp 2674 Tablets in Older Puppies).

   M. Kohlenberg of Shawnee Mission, Kansas conducted a study in 16 male and female Labrador Retriever puppies, which were 19 to 28 1/2 weeks of age. The 68 mg tablet was administered orally at daily doses of 5 (use rate), 15 (3X) or 25 (5X) mg/kg (2.27, 6.80 or 11.34 mg/lb) for 30 consecutive days. Four puppies served as controls. Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histology. Clinical signs of lameness were observed in the 25 mg/kg (11.34 mg/lb) treated group. Histological lesions of the articular cartilage were observed in all treatment groups and the effects were dose related. No treatment related trends occurred in the clinical chemistry or hematology parameters. A further trend was confirmed in that the 28 1/2-week old puppies were considerably less affected than the 19-or 21-week old animals.

5. General Safety Evaluation in Two Month Old Puppies (Safety Evaluation for the Use of BAY Vp 2674 Tablets in Puppies Approximately Two Months of Age).

   M. Kohlenberg of Shawnee Mission, Kansas conducted a controlled study in I6 male and female Beagle puppies, which were 7 1/2 to 8 1/2 weeks of age. The 5.7 mg tablet was administered for 30 consecutive days at daily rates of 5, 15 or 25 mg/kg (2.27, 6.80 or 11.34 mg/lb). Four puppies served as non-treated controls. Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histology. No clinical signs were observed except in the 25 mg/kg (11.34 mg/lb) group which showed a hyperextension of the carpal joints. No trends occurred in the clinical chemistry or hematology parameters No lesions were noted at necropsy. Microscopic lesions of the femoral articular cartilage were present in all treatment groups. The study concluded that side effects can be induced in puppies when treatment is initiated at 2 months of age.

6. General Safety Evaluation in Eight Month Old Puppies (Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Dogs. Approximately Eight Months of Age)

   M. Kohlenberg of Shawnee Mission, Kansas also conducted a controlled study in 16 male and female Beagle dogs, which were 8 months of age. The 22.7 mg tablet was given orally for 30 consecutive days at daily doses of 5, 15 or 25 mg/kg (2.27, 6.80 or 11.34 mg/lb). Four animals were controls. Evaluations were conducted for clinical signs, body weights, clinical chemistries, hematology, necropsy and histology. No significant clinical signs were observed and body weights remained stable. No trends developed in the clinical chemistry or hematology parameters. No treatment related gross or microscopic lesions were observed. This study concluded that treatment of 8 month old dogs is acceptable with daily doses of 25 mg/kg (11.34 mg/lb) for 30 consecutive days.

B. Corroborative Studies

Corroborative safety studies for the oral use of enrofloxacin (BAY Vp 2674) were conducted at Miles Laboratories, Elkhart, Indiana and Mobay Corporation, Animal Health Division. Shawnee Mission. Kansas as per Good Laboratory Practice

Regulations. Additionally, clinical field trial safety studies were conducted by 16 veterinary practitioners in various geographical areas of the United States.

1. Subchronic Feeding Study (Safety Evaluation of BAY Vp 2674: Subchronic Thirteen Week Feeding Study in Dogs).

   M. Porter of Elkhart, Indiana conducted a controlled study in 32 young adult, male and female, Beagle dogs for 13 weeks, with technical drug substance incorporated into the diet at rates equivalent to 0, 9.1, 22.5 and 52.0 mg/kg (0, 4.1, 10.2 and 23.6 mg/lb). Parameters included body weights, food consumption, clinical signs, clinical pathology, physical examinations, ophthalmoscopy, gross necropsy and histopathology. The study concluded that no significant effects were observed at any of the treatment rates.

2. Preliminary Safety Evaluation in Young Puppies (Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Puppies).

   M. Kohlenberg, under the direction of J. Shmidl, Shawnee Mission. Kansas, conducted a preliminary study in 12 mixed breed, male and female puppies which were from 6 weeks to 3 months of age. Four puppies received a daily oral dose of 10 mg/kg (4.5 mg/lb), 4 received 20 mg/kg (9.1 mg/lb) and 4 were nontreated controls. Treatments were for 14 consecutive days with the 22.7 mg tablet. Parameters were clinical signs, clinical chemistries, hematology, necropsy and histology. Some transient vomition occurred, but no adverse effects were seen in other parameters.

3. Safety in Heartworm Infected Dogs (Safety Evaluation for the Use of BAY Vp 2674 in D. immitis Microfilaria-Positive Dogs)

   M. Kohlenberg of Shawnee Mission, Kansas evaluated the oral treatment with 68 mg tablets using 9 adult, male and female dogs of various breeds which were microfilaria positive. Three received 5 mg/kg/day (2.27 mg/lb) for 10 days. 3 received 15 mg/kg/day (6.80 mg/lb) for 30 days and 3 were controls. Microfilaria counts were monitored with no trends developing in counts and necropsy revealed living adult heartworms in all 9 dogs. The study concluded safety for treatment of heartworm positive dogs with enrofloxacin.

4. Drug Interaction Study (Safety Evaluation for Concurrent Treatment of Puppies with BAY Vp 2674 Oral Tablets and Other Commonly Used Canine Health Products).

   M. Kohlenberg of Shawnee Mission, Kansas used 12 male and female mixed breed puppies which were 5 to 7 1/2 weeks of age they were given the 5.7 mg tablet orally for 10 days at a daily rate of 10 mg/kg (4.5 mg/lb). Concurrent treatments were anthelmintics (praziquantel, febantel, sodium disophenol), an insecticide (pyrethrin), another antibiotic (ampicillin) as well as common puppy vaccines and an injectable vitamin preparation. Parameters evaluated during the 21 day controlled study were clinical signs, body weights, clinical chemistries and hematology. The study concluded no adverse effects in puppies for concurrent treatment with these specific products and enrofloxacin.

5. Drug Interaction Study (Safety Evaluation for Concurrent Treatment of Dogs with BAY Vp 2674 Oral Tablets and Other Commonly Used Canine Health Products).

   M. Kohlenberg of Shawnee Mission, Kansas further evaluated concurrent compatibility in 12 male and female, various breed adult dogs. They were given the 68 mg tablet orally at a daily rate of 10 mg/kg (4.5 mg/lb) for 10 days in conjunction with other antibiotics (gentamicin sulfate, penicillin, dihydrostreptomycin), an insecticide (fenthion) and a heartworm preventative (styrylpyridinium chloride and diethylcarbamazine). This controlled study evaluated clinical signs, body weights, clinical chemistries, hematology and cholinesterase (plasma and red blood cell). The findings of the study concluded safety for concurrent treatment of dogs with enrofloxacin and the above specified drugs.

6. General Safety Evaluation (Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Puppies)

   M. Kohlenberg of Shawnee Mission, Kansas evaluated in a controlled study, the oral treatment with the 5.7 mg tablet in 16 male and female puppies of various breeds which were 1 1/2 to 15 weeks of age. Treatment schedules were 5 mg/kg/day (2.27 mg/lb/day) for 10 days and 15 or 25 mg/kg/day (6.80 or 11.34 mg/lb/day) for 30 days. Parameters included clinical signs, body weights, serum chemistries, hematology, necropsy lesions and histology. No adverse effects occurred in the study except for clinical overextension of the carpus joint in some of the 15 week old puppies following the higher treatments. The study concluded that no side effects occurred in 1 1/2 to 2 1/2 week old puppies following daily treatment at 25 mg/kg (11.34 mg/lb) for 30 consecutive days.

7. Safety Evaluation with Calcium and Phosphorous Supplementation (Additional Safety Evaluation for the Use of BAY Vp 2674 in Puppies).

   M. Kohlenberg of Shawnee Mission, Kansas used 18 mixed breed, male and female, puppies which were 19 to 24 weeks of age to evaluate the effect of a commercial calcium/phosphorous supplement in preventing clinical signs of lameness previously observed at higher treatment rates. The 68 mg enrofloxacin tablet was administered orally for 30 consecutive days at a rate of 25 mg/kg/day (11.34 mg/lb/day) in this controlled study. No beneficial effect in preventing clinical signs in this age group of rapid growth breeds was derived from the supplementation

8. Safety Evaluation with Magnesium Supplementation (Further Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Dogs).

   M. Kohlenberg of Shawnee Mission, Kansas used 12 male and female dogs of various breeds and with an age range of 29 1/2 to 34 weeks in a controlled study to evaluate the effects of magnesium supplementation in preventing clinical signs of lameness previously observed. Oral treatment was at the rate of 25 mg/kg (11.34 mg/lb) for 30 days with the 68 mg tablet. No clinical signs of lameness were observed in any of this age of dog even without the magnesium supplement.

9. General Safety Evaluation (General Safety Evaluation for the Use of BAY Vp 2674 Tablets in Younger Puppies).

   M. Kohlenberg conducted a controlled study with the 22.7 mg oral tablet in 15 Labrador Retriever male and female puppies which were 12 1/2 to 15 1/2 weeks of age. Treatment rates were 2.5, 7.5 and 12.5 mg/kg/day (1.13, 3.40 and 5.67 mg/lb/day) for 30 days or 15 mg/kg/day (6.80 mg/lb/day) for 15 consecutive days. Parameters included clinical signs, body weights, clinical chemistries, hematology, necropsy and histology. Clinical signs of lameness were observed in the puppies receiving the 12.5 and I5 mg/kg (5.67 and 6.80 mg/lb) treatments with cartilage lesions also observed in the 7.5 mg/kg (3.40 mg/lb) treated group.

10. General Safety Evaluation (General Safety Evaluation for The Use of BAY Vp 2674 Tablets in Rapidly Growing Younger Pups).

    M. Kohlenberg of Shawnee Mission, Kansas, further evaluated use of the 22.7 mg oral tablet at treatment rates of 10 mg/kg/day (4.5 mg/lb) for either 10 or 14 days in various large type breed puppies. The 12 male and female puppies were 10 to 12 weeks of age. This controlled study confirmed this dosage rate can induce abnormal carriage of the foreleg and histological lesions of the articular cartilage in this age of rapidly growing large type breeds of dogs.

11. Confirmation of Safety in Clinical Field Trial Safety.

    Confirmation of safety for the oral use of enrofloxacin tablets in dogs was achieved in clinical field trials. Sixteen veterinary practitioners located in various geographical areas of the United States conducted the safety evaluations. The enrofloxacin tablet formulations were administered to 270 dogs. Breeds of dogs treated were quite representative of the United States canine population. No breed susceptibility was observed. Weight range for the treated animals was 2.5 to 119 lb. Body weight was not a factor for safety.

    Age of animals receiving treatment was again representative with a range of 6 weeks to 15 years. No age susceptibility was observed.

    Numerous health products (for uses other than antimicrobial activity) were administered concurrently with enrofloxacin. These included a diuretic, urine acidifier, flea control shampoo, dip for mange, intravenous fluids, thyroid therapies, anesthetics and vaccines. No evidence of potentiation of any hazard to the dogs was observed in these cases.

    Two of the 270 (0.7%) treated with enrofloxacin tablets in the clinical field trials exhibited side effects, which were apparently drug related. These 2 cases of vomition were self-limiting. Other side effects observed during the clinical field trials were judged to probably not be drug related. These observations were classified as mild, self-limiting and consisted of 2 incidents of vomition, 2 of depressed appetite and 2 of either diarrhea or soft stool.

    In conclusion, the clinical field trial safety evaluations substantiated an adequate safety margin for the oral treatment of dogs with enrofloxacin if used as per the proposed label.

IV. 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 NADA. The drug is labeled for use in dogs, which are nonfood animals.

B. Human Safety Relative to Possession, Handling and Administration:

The labeling contains an adequate warning statement: "WARNING: Keep out of reach of children. Wash hands thoroughly with soap and warm water immediately after handling."

V. AGENCY CONCLUSIONS

The data submitted in support of this 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 tests to demonstrate safety to the target animal. Dermal infections (wounds and abscesses) caused by susceptible strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Staphylococcus aureus*.

Respiratory infections (pneumonia, tonsilitis, 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.

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.

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