Date of Approval: March 25, 2010

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-305

ORBAX Oral Suspension

orbifloxacin
Cats and Dogs

For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Staphylococcus aureus, Escherichia coli*, and *Pasteurella multocida*

For the treatment of urinary tract infections (cystitis) in dogs caused by susceptible strains of *Staphylococcus pseudintermedius, Proteus mirabilis, Escherichia coli* and *Enterococcus faecalis.* ORBAX Oral Suspension is also indicated for skin and soft tissue infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus pseudintermedius, Staphylococcus aureus,* coagulase positive staphylococci, *Pasteurella multocida, Proteus mirabilis, Pseudomonas* spp.*, Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp.*, Citrobacter* spp.*, Enterococcus faecalis,* β-hemolytic streptococci (Group G) and *Streptococcus equisimilis.*

Sponsored by:

Intervet, Inc.

I. GENERAL INFORMATION: CATS

A. File Number:	NADA 141-305
B. Sponsor:	Intervet, Inc. 56 Livingston Ave. Roseland, NJ 07068 Drug Labeler Code: 000061
C. Proprietary Name(s):	ORBAX Oral Suspension
D. Established Name(s):	Orbifloxacin
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Oral suspension
G. Amount of Active Ingredient(s):	30 mg/mL of orbifloxacin
H. How Supplied:	20 mL bottle
I. How Dispensed:	Rx
J. Dosage(s):	In the cat, ORBAX Oral Suspension and ORBAX Tablets are not bioequivalent. On a mg/kg basis, ORBAX Oral Suspension provides lower and more variable plasma levels of orbifloxacin than ORBAX Tablets (See Clinical Pharmacology and Precautions). The dose of ORBAX Oral Suspension in the cat is 3.4 mg/lb (7.5 mg/kg) of body weight administered once daily. DO NOT EXCEED 3.4 mg/lb (7.5 mg/kg) BODY WEIGHT PER DAY IN CATS.
K. Route(s) of Administration:	Oral
L. Species/Class(es):	Cats
M. Indication(s):	For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Staphylococcus aureus*, *Escherichia coli*, and *Pasteurella multocida*

II. EFFECTIVENESS:

A. Dosage Characterization:

The data in support of a 7.5 mg/kg daily dose of ORBAX Oral Suspension for cats was based upon three pharmacokinetic investigations:

- Comparison of Orbifloxacin in Oral Liquid to ORBAX Tablets in a Biocomparable, Crossover Study in Cats (Study # 99379).

- Single and Multiple Dose Pharmacokinetic Profile of Orbifloxacin (SCH 51854) Administered in ORBAX Oral Liquid to Cats at a Dose of 7.5 mg/kg Once Daily for Five Days (Study # 39669).

- Exploratory Determination of the Single Dose Plasma Pharmacokinetics of Orbifloxacin Dosed at 7.5 mg/kg in ORBAX Oral Liquid in Fed and Fasted Cats (Study # 35714).

The dosage characterization was based upon the blood levels observed following a single dose of the oral suspension administered to fasted cats at a rate of 7.5 mg/kg that were obtained from the three studies above. A summary of the study designs associated with this pharmacokinetic-pharmacodynamic (PK-PD) assessment are provided in Table 1 below:

Table 1. Studies used to support the effectiveness of ORBAX Oral Suspension

Study Report	# cats	Dose	Design	prandial state	Blood sampling time (hr)	Assay
99379	24	7.5 mg/kg	cross-over/tablet-suspension 27 day washout	fast 6 hrs pre/ 4 hrs post	0.5, 1, 2, 3, 4, 6, 8, 16, 24	HPLC
39669	12	7.5 mg/kg	daily for 5 days	fast 6 hrs pre/ 4 hrs after	0.5, 1, 2, 3, 4, 6, 8, 16, 24	HPLC
35714	6	7.5 mg/kg	cross-over/fed-fast 2 day washout	fed- 1hr pre; fast 6 hrs pre/ 4 hrs post	0.5, 1, 2, 3, 4, 6, 8, 16, 24	HPLC

The results obtained in the individual studies are provided in Table 2.

Table 2. Individual study results

Study	Formulation	**$AUC_{0\text{-last}}$ *,a** µg*hr/mL (± SD)	**$AUC_{0\text{-inf}}$ *,a** µg*hr/mL (± SD)	**Cmax *,a** µg/mL (± SD)	**Tmax *,a** hr (range)	**T½ *,b** hr (± SD)	**Conclusions**
99379	Tablet	33.0 (8.9)	36.4 (8.5)	4.3 (1.2)	0.6 (0.5-1.0)	5.2 (1.5)	Bioavailability of 7.5 mg/kg dose of the tablets is greater than the 7. 5 mg/kg dose of the oral suspension, but the latter did exceed the blood levels observed following a 2.5 mg/kg dose of the tablet.
	Suspension	26.7 (8.4)	30.4 (7.7)	2.9 (1.4)	1.8 (0.5-8.0)	6.2 (2.4)	
35714	Fed	37.3 (14.5)	42.1 (15.1)	3.4 (1.3)	3.8 (1.0-8.0)	8.04 (3.5)	Food leads to a slight increase in the bioavailability of ORBAX Oral Suspension in most cats.
	Fasted	26.4 (5.7)	31.6 (8.3)	3.0 (0.6)	1.6 (0.5-3.0)	9.43 (2.4)	
39669	Dose 1 of Multi-dose study	33.0 (10.0)	42.0 (15.0)	3.2 (0.9)	2 (0.5-4.0)	10.0 (3.0)	

***** $AUC_{0\text{-last}}$ = the area under the concentration versus time curve from time zero to the last quantifiable concentration during the first 24-hr dosing period
$AUC_{0\text{-inf}}$ = AUC from time zero and extrapolated to time infinity
C_{max} = peak observed drug concentration
T_{max} = time to C_{max}
T½ = terminal elimination half life
[a]= arithmetic mean
[b] = harmonic mean

B. Substantial Evidence:

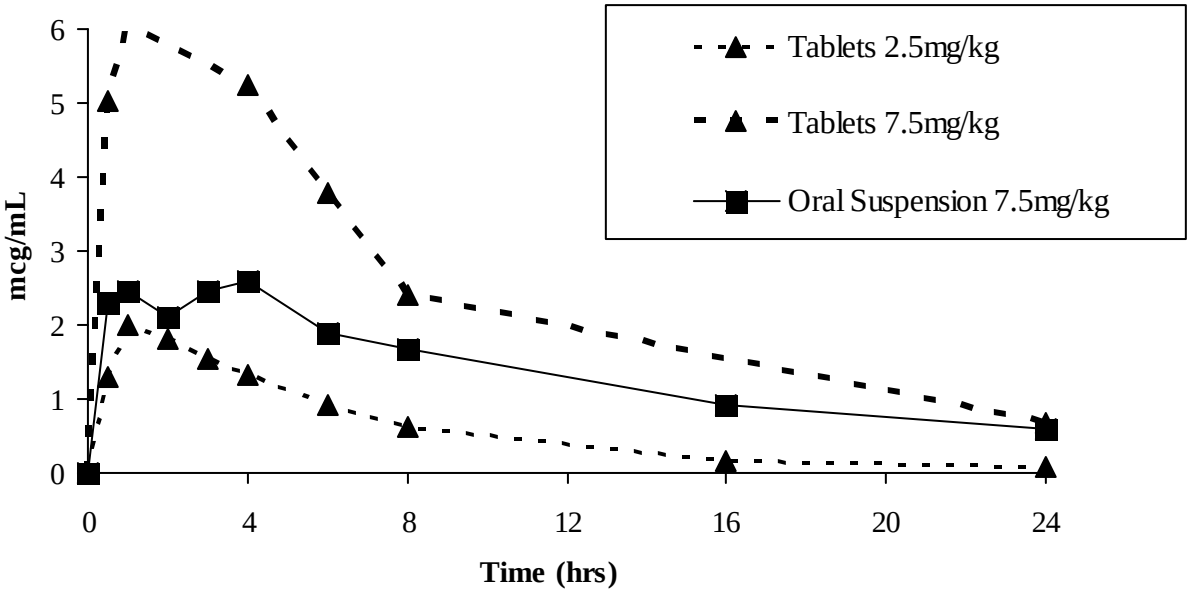
Because the approved tablets and the oral suspension formulation are not bioequivalent, the effectiveness of the oral suspension was based upon the effectiveness of the 2.5 mg/kg tablet dose used in the original field study (See the original FOI Summary for NADA 141-081 approved September 18, 1997) and a PK-PD assessment of the free orbifloxacin plasma concentrations obtained following a single 7.5 mg/kg oral suspension dose under fasted conditions. The MIC values used in this assessment were derived from the original tablet field study. From the three studies listed in Table 2, at least 90% of the cats receiving a 7.5 mg/kg dose of the oral suspension succeeded in meeting the PK-PD target of free drug AUC/MIC $\geq$ 40 hr for *S. aureus* (range of MIC values obtained during the original tablet field study was 0.195 – 0.39 µg/mL; MIC_{90} not available) and *P. multocida*[1] (MIC_{90} = 0.048

[1] PK-PD target of AUC/MIC of 40 hr for *P. multocida* was based upon information provided by Schering-Plough Animal Health Corp.

µg/mL*)*. The PK-PD target for *E. coli* (AUC/MIC $\geq$ 100 hr) was also achieved in 90% of the cats (MIC_{90} = 0.19 µg/mL). Based upon this information, it was concluded that 7.5 mg/kg oral dose of ORBAX Oral Suspension would be as effective as a 2.5 mg/kg dose of ORBAX Tablets.

The relative drug concentrations observed after a single 7.5 mg/kg dose of ORBAX Tablets and oral suspension and after a 2.5 mg/kg dose of ORBAX tablets are provided in Figure 1.

Figure 1: Relative drug concentrations following a dose of oral suspension versus tablet formulations. (Orbifloxacin plasma concentrations (mcg/mL) following single oral administration of the ORBAX Tablet and ORBAX Oral Suspension formulations)



Pharmacokinetic Assessment

1. Assessment: A cross-study PK-PD assessment of orbifloxacin exposure following a 7.5 mg/kg daily dose of ORBAX Oral Suspension was conducted. The data generated in the three pharmacokinetic studies described under Dosage Characterization were used to determine if the unbound (free) plasma concentrations of orbifloxacin following a 7.5 mg/kg daily dose of ORBAX Oral Suspension are consistent with the PK-PD targets supporting product effectiveness. Effectiveness was based upon the pharmacokinetic data generated after a single fasted dose in 41 cats (One cat in study #99379 did not provide any information on the oral suspension). The criteria used in this PK-PD assessment are defined above.

2. Results: The results of this analysis are summarized in Table 3.

Table 3. Cross-study PK/PD determination supporting product effectiveness (n = 41).

	$AUC_{0\text{-last}}$*	**Cmax**	**$AUC_{0\text{-inf}}$**	Corrected for protein binding		
				$AUC_{0\text{-last}}$ /MIC	**Cmax/MIC**	**$AUC_{0\text{-inf}}$ /MIC**
If MIC = 0.39 µg/mL (*S. aureus*)**						
Mean	28.5	3.0	33.4	59.9	6.3	71.4
%CV	31.7	38.6	34.9	31.7	38.6	33.5
If MIC = 0.19 µg/mL (*E. coli*)**						
Mean				119.8	12.7	142.9
%CV				31.6	38.5	33.5

* where $AUC_{0\text{-last}}$ is estimated from time zero to the last quantifiable concentration observed during the first 24-hour dosing interval.
** MIC data from NADA 141-081 approval for ORBAX Tablets in cats.

3. Conclusions: The data indicate that a 7.5 mg/kg dose of ORBAX Oral Suspension succeeds in meeting the PK-PD targets[2] for clinical success for *P. multocida*, *E. coli*, and *S. aureus* in at least 90% of the cats included in this evaluation.

Protein binding study

1. Study Title: *In Vitro* Binding of SCH 51854 (Orbifloxacin) to Cat Plasma Protein Using Ultrafiltration

2. Type of Study: Pharmacokinetic study

3. General Design:

   a. *Purpose:* The objective of this study was to evaluate cat plasma protein binding by ultrafiltration at 37°C, using Centrifree micropartition devices. The concentration of SCH 51854 in cat plasma and ultrafiltrate (UF) was determined using HPLC-MS/MS by the Drug Safety & Metabolism-Animal Health Group (Lafayette, NJ) at SPRI.

4. Results: See Table 4.

[2] CLSI. Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents: Approved Guideline – Third edition. CLSI document M37-A3. Wayne, PA: Clinical Laboratory Standards Institute; 2008.

Table 4. Orbifloxacin binding to feline plasma proteins.

Nominal Orbifloxacin (µg/mL)	Mean Orbifloxacin Plasma Protein Binding
0.1	17.3%
1	18.8%
10	18.4%

5. Conclusion: ORBAX (orbifloxacin) Oral Suspension has low protein binding (~18%) in feline plasma.

Palatability study

1. Study Title: Efficacy, Safety and Palatability of Orbifloxacin Liquid Administered Orally, in the Management of Dermal Infection in Cats Associated with Bacteria Susceptible to Orbifloxacin (France, Belgium, Germany 2001).

2. Type of Study: Field palatability study

3. General Design:

   a. *Purpose:* The objective of this study was to demonstrate the palatability of ORBAX Oral Suspension administered orally for the treatment of wounds and abscesses in client-owned cats.

   b. *Test Animals*: Intact or neutered, pure or mixed breed male, and non-pregnant female, client-owned cats, 12 weeks of age and older, presented for veterinary care to 21 investigators in France, Belgium and Germany were enrolled.

   c. *Number of Test Animals:* One hundred and one cats received treatment with ORBAX Oral Suspension.

   d. *Control and Treatment Group:* For the purpose of evaluating palatability, a control group was not used. Acceptance and non-acceptance were reported as percentages of the total number of cats treated with the test article.

   Table 5. Treatment Groups

Treatment Group	Dose (mg/kg) for up to 10 days	Number of Animals
ORBAX Oral Suspension	7.5 mg/kg (1 mL/kg)	101

e. Drug Administration:

i. Dosage amount, frequency, and duration: ORBAX Oral Suspension (30 mg/mL orbifloxacin) was administered at 7.5 mg/kg (1 mL/kg) once daily for up to 10 days.

ii. Route of administration: Oral

iii. Other Comments: The test article was administered directly into each cat's mouth using a syringe graduated in 0.2 mL increments. The test article was administered on Day 1 by the treatment administrator, and on subsequent days, by the owner.

f. Parameters measured:

Palatability was scored on Day 1 by the treatment administrator and on subsequent treatment days by the owners. The following scoring descriptions were employed:

0 = Non-acceptance: Repeated negative reactions such as: pawing at the mouth, excessive salivation, retching, vomiting, spitting, drooling or gagging.

1 = Acceptance: Acceptance of the test article without displaying negative reactions.

4. Results:

An overall evaluation of the palatability for the entire treatment period was determined by the owner at the end of the treatment period. An explanation of the palatability criteria was provided to the owner.

Acceptance and non-acceptance were reported as percentages of the total number of cats treated with the test article. For the Day 0 palatability assessment by the treatment administrator, 95% (96/101) of cats treated with ORBAX Oral Suspension demonstrated acceptance.

The overall palatability assessment made by the cat owners for the entire duration of the treatment showed that 95% (96/101) of the cats treated with ORBAX Oral Suspension demonstrated acceptance. This calculation includes 2 cats that did not return for the second clinical visit.

5. Conclusion: ORBAX Oral Suspension was accepted by 95% of the cats following oral administration.

III. TARGET ANIMAL SAFETY:

A. Target Animal Safety Study

1. Study Title: "Orbifloxacin (SCH 51854): Oral Liquid 1-Month Target Animal Safety Study in Cats", Study No.: 99549

2. Type of Study: 30-day feline oral safety study

3. Study Director: Patricia Turk
   MPI Research, Inc.
   Mattawan, MI 49071-9399

4. General Design:

   a. Purpose: The objective of this study was to evaluate the safety of orbifloxacin when administered orally as ORBAX Oral Suspension to cats at 2, 6, and 10X the dose of 7.5 mg/kg/day for 30 consecutive days, compared to a control (placebo).

   b. Animals: Thirty-two (32) healthy cats (16 males and 16 females) were randomly assigned to four treatment groups of 4 cats/sex/group. Cats were at least 5.5 to 7 months of age at the time of initiation of dosing.

   c. Placebo Control: Distilled water

   d. Dosage Form: ORBAX Oral Suspension (30 mg of orbifloxacin/mL suspension).

   e. Dosage Used:

   Table 6. Dosing Groups

Dose (mg/kg/day)	Dose Volume (mL/kg/day)
0	2.5
15.0 (2X)	0.5
45.0 (6X)	1.5
75.0 (10X)	2.5

   f. Route of Administration: Oral (the 45.0 and 75.0 mg/kg-dosed groups were dosed by oral gavage).

   g. Study Duration: Thirty days

   h. Pertinent Measurements/Observation: The following observations were performed during the study: clinical observations, physical examination, food and

water consumption, body weight, ophthalmic exams, electroretinographic (ERG) exams, electrocardiographic analysis, hematology, blood chemistry, urinalysis, organ weights, histopathology, orbifloxacin plasma concentrations, and taurine analysis.

i. *Data Analysis:* All continuous variables were analyzed using a repeated measures analysis of variance or covariance. The statistical model included the fixed effects of treatment, sex, and day, and all interactions. Pretreatment observations or the observation deviations from the subclass mean were considered as a possible covariate for each of the variables. Least square means were used to compare treatment groups. Ordinal data were summarized using contingency tables and treatment groups were compared using the Cochran-Mantel- Haenszel statistic.

5. Results:

One death occurred during this study; it appeared to be an anesthetic death following anesthesia for an electroretinogram.

Hematology: Leukocytosis with neutrophilia was seen in three treated animals (one 10X and two 2X) and a marked leukopenia was seen in one 2X animal.

Clinical Chemistries: Two cats had decreases in albumin levels that may be clinically significant; a 10X cat had an albumin decrease to <1.5 g/dL by Day 30 (normal 2.5-3.5 g/dL) and a 6X cat (the cat died during the study) had an albumin level that decreased to 2.5 g/dL. The albumin decrease was statistically significant in the 10X dose group ($p = 0.0648$) and the albumin/globulin ratios were statistically significantly decreased in the 6X ($p = 0.0495$) and 10X dose groups ($p = 0.0103$).

An elevated globulin level was seen in one 6X and two 10X animals. The 10X cat with the lowest albumin level also was one of the 10X females that was anorexic and did not gain weight. These two 10X cats also had lymphoid hyperplasia and a hemorrhagic pancreas at necropsy.

Elevated liver enzymes were seen sporadically in several cats (one control, three 2X and two 10X). Decreased alkaline phosphatase (ALP) levels were seen in the 10X females. Marked liver enzyme elevations seen in a 10X cat consisted of an elevated aspartate aminotransferase (AST) of 56 U/L (normal 14-30 U/L) and an elevated alanine transaminase (ALT) of 642 U/L (normal 42-86 U/L) on Day 21. The elevated liver enzymes returned to normal by Day 30; this cat also had a mild increase in globulin level and a leukocytosis with a neutrophilia on Day 30. Decreased alkaline phosphatase (ALP) levels were statistically significant in the 10X group as compared to the control group. There was a statistically significant increase in the creatinine of the 2X dose group ($p = 0.0336$) compared to that of the control group.

Observations: There was an increased incidence of vomiting and hypersalivation in the 6X and 10X dose groups. Soft, mucoid feces and fecal discoloration were seen in all dose groups, with a slightly higher incidence in the treated groups, especially the 10X group.

An increased incidence of lacrimation was seen in treated animals, most noticeable in the 10X group. Test article related reduction in food consumption and body weights was noted in the 10X females.

Ophthalmic examination findings: Ophthalmic abnormalities were related to treatment with orbifloxacin. By Day 24 of treatment, lesions of hyperreflectivity indicative of central retinal degeneration were seen in multiple animals in the 6X and 10X dose groups. By Day 30, sluggish pupillary light reflexes or incomplete pupil constriction were also seen in the 6X and 10X dose groups. In the 2X dose group, one animal had hyperreflectivity of the area centralis, indicative of stage II retinal degeneration in the left eye, although no lesions were seen on histopathology. The ERG results in all of the cats showed that there was some functioning retina. On histopathology and electron microscopy, microscopic lesions were seen in the 6X and 10X dose groups. Lesions consisted of swollen cell bodies in the outer nuclear layer, and/or disorganized disc material in the outer photoreceptor segments. In addition, photoreceptor cell atrophy and Mueller cell hypertrophy were seen in one 10X female. The altered tapetal reflectivity is likely due to disarrayed disc material in the photoreceptor outer segments.

Taurine deficiency was eliminated as a possible cause for central retinal degeneration in these cats.

Pathology: One cat (6X) had a pale liver at necropsy with vacuolation on histopathology.

6. Conclusion:

Test article-related tapetal hyperreflectivity which correlated histopathologically with minimal photoreceptor swelling was noted in cats at 45.0 and 75.0 mg/kg/day doses. There was an increased incidence of lacrimation during the study in males at 45.0 mg/kg/day and in both sexes at 75.0 mg/kg/day. Decreased food consumption and decreased body weight were also noted in females at 45.0 mg/kg/day and in both sexes at 75.0 mg/kg/day. One 15 mg/kg cat had hyperreflectivity of the area centralis, indicative of stage II retinal degeneration in the left eye, although no lesions were seen on histopathology.

Additional test article-related findings included vomiting and increased salivation in the 6X and 10X groups (45 and 75 mg/kg groups, respectively). An increased incidence of soft, mucoid, and/or watery feces was seen in the 75 mg/kg group. A decrease in serum alkaline phosphatase was observed in the 10X females. Decreased

serum albumin was noted in 1 female that received 75.0 mg/kg/day, with a corresponding decrease in serum calcium.

B. Ocular Safety Study

1. Study Title: Orbifloxacin (SCH 51854): Oral suspension 30-Day Target Animal Ocular Safety Study in Cats; Study No. 01141

2. Type of Study: 30-day feline ocular safety study

3. Study Director: Patricia Turk
   MPI Research, Inc.
   Mattawan, MI 49071-9399

4. General Design:

   a. *Purpose:* The objective of this study was to evaluate the ocular safety of orbifloxacin when administered as ORBAX Oral Suspension to cats at doses of 0 and 7.5 mg/kg/day, for at least 30 consecutive days.

   b. *Animals:* Sixteen (16) healthy cats (8 males and 8 females) were randomly assigned to two treatment groups of 4 animals/sex/group. Cats were at least 5 to 6 months of age at the time of initiation of dosing.

   c. *Placebo Control:* Distilled water

   d. *Dosage Form:* ORBAX Oral Suspension (30 mg of orbifloxacin/mL suspension).

   e. *Dosage Used:*

Table 7. Dosing Groups

Dose (mg/kg/day)	Dose Volume (mL/kg/day)
0	0.25
7.5 (1X)	0.25

   f. *Route of Administration:* Oral

   g. *Study Duration:* Thirty days

   h. *Pertinent Measurements/Observation*: The following observations were performed during the study: clinical observations, physical examination, ophthalmic exams, electroretinographic (ERG) exams, ocular histopathology, and orbifloxacin plasma concentrations.

5. Results:

   Observations: An increased incidence was seen in soft feces in the male treated animals compared to the control animals. An increased incidence of decreased fecal production was seen in treated females.

   Ophthalmic examination findings: Three cats (one control and two treated cats) exhibited a metallic sheen on retinal examination; no functional or structural pathology was observed.

   Ocular histopathology: One treated cat had a focal, tiny area of minimal photoreceptor degeneration in the retina of one eye. This area of retinal degeneration/disorganization was characterized by disruption of a few of the photoreceptors in the photoreceptor layer associated with a few plump retinal pigmented epithelial cells. This finding is in contrast to the retinal degeneration lesions found in the previous study at the higher doses (where swollen photoreceptor cell bodies were observed in many different areas of the retina in many cats).

6. Conclusion: At the 7.5 mg/kg dose, one cat had minimal focal retinal degeneration/disorganization seen on histopathology; whether this finding is treatment related is unknown. Soft feces were observed in some treated cats.

IV. GENERAL INFORMATION: DOGS

A. File Number:	NADA 141-305
B. Sponsor:	Intervet, Inc. 56 Livingston Ave. Roseland, NJ 07068 Drug Labeler Code: 000061
C. Proprietary Name:	ORBAX Oral Suspension
D. Established Name:	Orbifloxacin
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Oral suspension
G. Amount of Active Ingredient:	30 mg/mL of orbifloxacin
H. How Supplied:	20 mL bottle
I. How Dispensed:	Rx
J. Dosage(s):	The dose of ORBAX Oral Suspension in the dog is 1.1 to 3.4 mg/lb (2.5 to 7.5 mg/kg) of body weight administered once daily. For the treatment of skin infections (wounds and abscesses), ORBAX Oral Suspension should be given for two (2) to three (3) days beyond the cessation of clinical signs for a maximum of 30 days. For the treatment of urinary tract infections, ORBAX Oral Suspension should be administered for at least 10 consecutive days.
K. Route of Administration:	Oral
L. Species/Class(es):	Dogs
M. Indication(s):	For the treatment of urinary tract infections (cystitis) in dogs caused by susceptible strains of *Staphylococcus pseudintermedius, Proteus mirabilis, Escherichia coli* and *Enterococcus faecalis* and skin and soft tissue infections (wounds and abscesses) in dogs caused by

susceptible strains of *Staphylococcus pseudintermedius, Staphylococcus aureus,* coagulase positive staphylococci, *Pasteurella multocida, Proteus mirabilis, Pseudomonas* spp., *Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Citrobacter* spp., *Enterococcus faecalis,* β-hemolytic streptococci (Group G) and *Streptococcus equisimilis.*

V. EFFECTIVENESS:

A. Dosage Characterization:

The ORBAX Tablet (NADA #141-081 approved April 22, 1997) oral dose of 2.5 to 7.5 mg/kg bodyweight administered once daily, previously established to be effective for treatment of certain urinary tract infections and skin and soft tissue infections (as described under indications), was selected for evaluation for the oral suspension formulation.

Pharmacokinetic data from a comparison of ORBAX (orbifloxacin) Oral Suspension to ORBAX Tablets in a relative bioavailability crossover study in dogs demonstrated that ORBAX Oral Suspension is bioequivalent to ORBAX Tablets (Bioequivalence Study # 99378).

B. Substantial Evidence:

1. Study Title: Bioequivalence Study (# 99378)

2. Type of Study: Pharmacokinetic study

3. Study Director: William F. Feely, M.S.
   Schering-Plough Research Institute
   Lafayette, NJ 07848

4. General design:

   a. *Purpose*: The objective of the study was to demonstrate the relative bioavailability of ORBAX Oral Suspension as compared to the currently approved ORBAX Tablets.

   b. *Test Animals*: Twenty-four (24) healthy, Beagle dogs (12 males and 12 females) approximately 11 months to 3 years of age and ranging in weight from 10 to 19 kg

   c. Dosage Form: ORBAX Oral Suspension and tablet formulations

   d. Route of Administration: Oral

e. *Dose and Frequency of Treatment:* Each of the two formulations of orbifloxacin was given at a target dose of 7.5 mg per kg orbifloxacin and each formulation was administered orally once to each group of animals (dose based on individual body weight).

f. *Study Design:* The study was performed as a randomized, two-period, two-sequence, two-treatment cross-over experiment. Study dogs were randomly assigned to two groups (I or II) of twelve dogs each. Initially, Group I dogs received a target dose of 7.5 mg/kg of orbifloxacin as ORBAX Tablets and Group II dogs received the ORBAX Oral Suspension formulation at the same target dose. Following a washout period of 14 days, the treatments were reversed between the two groups. Animals were fasted for at least 6 hours prior to dose administration and for at least 4 hours following dosing.

The products used in this study were as follows:

- Reference Formulation: A tablet formulation containing orbifloxacin at 5.7, 22.7 or 68 mg (ORBAX Tablets).
- Test Formulation: An oral suspension consisting of 30 mg of orbifloxacin per mL (ORBAX Oral Suspension).

g. *Pertinent Parameters Measured*: Blood samples were collected for orbifloxacin analysis prior to dosing and at 0.5, 1, 2, 3, 4, 6, 8, 16, and 24 hours following each dosing. Plasma, prepared from the blood samples, was analyzed by a validated High Performance Liquid Chromatography (HPLC) method using fluorescence detection to determine orbifloxacin concentrations.

h. *Study Duration:* 16 Days (including the 14-day washout period)

i. *Data Analysis:* The pharmacokinetic variables estimated in this investigation included the maximum observed concentration (C_{max}), the area under the curve to the last quantifiable time point (AUC_{last}), the area under the curve extrapolated to infinity (AUC_{∞}), and the dose normalized area under the curve (AUC_{∞}/dose). Sex-related differences in AUC_{last}, AUC_{∞}, AUC_{∞}/dose, and C_{max} values were considered within each formulation using a Student's t-test procedure. The absence of statistically significant differences across sexes allowed for the pooling of data generated across sexes for the purpose of estimating product relative bioavailability. Bioequivalence was statistically confirmed using the two one-sided test procedure for estimating the 90% confidence interval about the difference between treatment means (expressed relative to the reference mean for untransformed data) or the ratio of treatment means (log-transformed data). The pivotal pharmacokinetic metrics for the bioequivalence determination were AUC_{last} and C_{max}. As per CVM's Guidance Document # 35, Bioequivalence Guideline, the statistical criterion used for confirming product bioequivalence was the presence of confidence limits contained within the bounds of +/-20% (untransformed data) or 80 to 125% (log transformed data).

5. Results: The lower and upper confidence limits were contained within the bounds of +/- 20% for C_{max} and AUC_{last} (untransformed data), and were thus consistent with the criterion for product bioequivalence. Means and confidence interval boundary information for the pharmacokinetic variables C_{max}, AUC_{last}, AUC_{∞}, and AUC_{∞}/dose are summarized in Table 8.

Table 8. Summary of Results (Study number 99378)

Pharmacokinetic Variable	Mean[1]	90% Confidence Limits[2]	
		Lower Bound (%)	Upper Bound (%)
C_{max} (μg/mL)		- 13.66	- 2.13
ORBAX Tablets	6.32		
ORBAX Oral Suspension	5.82		
AUC_{last} (μg • hr/mL)		- 6.68	+ 4.61
ORBAX Tablets	55.19		
ORBAX Oral Suspension	54.62		
AUC_{∞} (μg • hr/mL)		- 6.35	+ 4.75
ORBAX Tablets	60.85		
ORBAX Oral Suspension	60.37		
AUC_{∞}/dose (μg • hr/mL)		- 6.72	+ 4.26
ORBAX Tablets	8.13		
ORBAX Oral Suspension	8.03		

[1] C_{max}, AUC_{last}, AUC_{∞} and AUC_{∞}/dose variables are presented as overall means for pooled male and female data (not transformed).
[2] Confidence limits = the lower and upper bounds of the ninety percent (90%) confidence interval expressed as differences in treatment means relative to the mean of the ORBAX Tablet formulation.

Although not considered pivotal to the study conclusions, the 90% confidence limits about the difference between product means were also determined for AUC_{∞} and AUC_{∞}/dose and were found to fall within the bounds of +/-20%. Log transformation of the data also demonstrated bioequivalence, as the 90% CI were between the acceptance criteria for transformed data of 80 to 125%.

6. Conclusions*:* Comparison of the C_{max}, $AUC_{last,}$ $AUC_{\infty,}$ and AUC_{∞}/dose of the tablet and oral suspension formulations, based upon the 90% confidence limits for the ratio of the oral suspension mean to the tablet mean, are consistent with statistical criteria for the demonstration of product bioequivalence. Accordingly, the data confirm that the ORBAX Oral Suspension formulation is bioequivalent to ORBAX Tablets in dogs. No adverse reactions were observed during this study.

Palatability study

1. Study Title: Efficacy, Safety and Palatability of Orbifloxacin Liquid Administered Orally, in the Management of Skin and Soft Tissue Infections Associated with Bacteria Susceptible to Orbifloxacin (France, Belgium, Germany 2000).

2. Type of Study: Field palatability study

3. General Design:

   a. *Purpose:* The objective of this study was to demonstrate the palatability of ORBAX Oral Suspension administered orally for the treatment of skin infections (wounds and abscesses) in client-owned dogs.

   b. *Test Animals:* Client-owned dogs, ranging from 0.7 years to 16 years of age, and weighing between 2.6 kg – 62 kg, presenting for veterinary care to investigators in France, Belgium and Germany were enrolled.

   c. *Number of Test Animals:* Eighty one dogs received treatment with ORBAX Oral Suspension.

   d. *Control and Treatment Group:* For the purpose of evaluating palatability, an active control group was used. An equal number of dogs were randomized to each treatment group. Acceptance and non-acceptance were reported as percentages of the total number of dogs treated with the test article.

Table 9. Treatment Groups

Treatment Group	Dose (mg/kg) for up to 10 days	Number of Animals
ORBAX Oral Suspension	7.5 mg/kg (1 mL/kg)	81

   e. *Drug Administration:*

      i. Dosage amount, frequency, and duration: ORBAX Oral Suspension (30 mg/mL orbifloxacin) was administered at 7.5 mg/kg (1 mL/kg) once daily for 4 to 12 days.

      ii. Route of administration: Oral

      iii. Other Comments: The test article was administered directly into each dog's mouth using a syringe graduated in 0.2 mL increments. The test article was administered on Day 1 by the treatment administrator, and on subsequent days, by the owner.

f. Parameters measured:

Palatability was scored on Day 1 by the treatment administrator and on subsequent treatment days by the owners. The following scoring descriptions were employed:

0 = Non-acceptance: Any negative reaction to the test substance including but not limited to pawing at the mouth, excessive salivation, retching, vomiting, spitting, drooling or gagging.

1 = Acceptance: Acceptance of the test article without displaying negative reactions.

4. Results:

An overall evaluation of the palatability for the entire treatment period was determined by the owner at the end of the treatment period. An explanation of the palatability criteria was provided to the owner.

Acceptance and non-acceptance were reported as percentages of the total number of dogs treated with the test article. For the Day 0 palatability assessment by the treatment administrator, 98.8% (80/81) of dogs treated with ORBAX Oral Suspension demonstrated acceptance.

The overall palatability assessment made by the dog owners for the entire duration of the treatment showed that 96.3% (78/81) of the dogs treated with ORBAX Oral Suspension demonstrated acceptance.

5. Conclusion: ORBAX Oral Suspension was accepted by 96.3% of the dogs following oral administration.

VI. TARGET ANIMAL SAFETY:

A. Target Animal Safety Study

1. Study Title: Orbifloxacin (SCH 51854) Oral Liquid 1-Month Target Animal Safety Study in Dogs (# 99548)

2. Type of Study: 30-day dog oral safety study

3. Study Director: Patricia Turk
   MPI Research, Inc.
   Mattawan, MI 49071-9399

4. General Design:

   a. *Purpose:* To assess the toxicity of orbifloxacin when administered orally as ORBAX Oral Suspension to Beagle dogs at doses of 1X, 3X and 5X the maximum anticipated clinical dose (7.5 mg/kg/day) for 30 consecutive days, and at 10X the maximum anticipated clinical dose for 10 consecutive days, compared to a control (placebo).

   b. *Animals:* Fifty (50) healthy, Beagle dogs (25 males and 25 females). The dogs were at least 9 months of age and weighed between 6.8 and 14.5 kg at the time of initiation of dosing.

   c. *Placebo Control:* Ten (10) control dogs (5 males and 5 females) were dosed orally with distilled water at 1.25 mL/kg (equivalent to the volume administered to the 5X treatment group) once daily for 30 days.

   d. *Dosage Form:* ORBAX Oral Suspension (30 mg of orbifloxacin/mL suspension).

   e. *Dose and Frequency of Treatment:* Dogs were administered ORBAX Oral Suspension at 7.5, 22.5, or 37.5 mg/kg once daily for 30 days. For the drug tolerance segment of the study, ORBAX Oral Suspension was administered to dogs at 75 mg/kg once daily for 10 days, by oral gavage. There were 10 dogs per treatment group (5 males and 5 females), and animals were dosed based on body weight.

   f. *Route of Administration:* Oral; Dogs in the 75 mg/kg treatment group were administered the test article by oral gavage.

   g. *Duration of Study:* 30 days

h. *Study Design:* Dogs were randomly assigned to five treatment groups consisting of 5 animals/sex/group. The investigators were not masked to treatment groups.

i. *Evaluation:* Pertinent parameters measured included clinical observations, physical examination, food consumption, water consumption, body weight, ophthalmic examination, electrocardiographic analysis, hematology, blood chemistry, urinalysis, and orbifloxacin plasma concentration analysis. At the end of the study, all animals were euthanized and necropsied, and the following parameters were evaluated: gross pathology, organ weights, and histopathology.

j. *Data Analysis:* All continuous variables were analyzed using a repeated measures analysis of variance or covariance. The statistical model included the fixed effects of treatment, sex, and day, and all interactions. Pretreatment observations or the observation deviations from the subclass mean were considered as a possible covariate for each of the variables. Least square means were used to compare treatment groups. Ordinal data were summarized using contingency tables and treatment groups were compared using the Cochran-Mantel- Haenszel statistic.

5. Results: ORBAX Oral Suspension was administered to young, clinically healthy, Beagle dogs at a dose of 7.5 mg/kg/day (1X), 22.5 mg/kg/day (3X) and 37.5 mg/kg/day (5X) once daily for 30 consecutive days and at 75 mg/kg/day (10X) once daily for 10 consecutive days. No mortality occurred during the study. Body temperature, respiratory rate and heart rate were not affected by orbifloxacin treatment. Discoloration of the feces was observed at all dose levels. At 37.5 and 75 mg/kg/day, ORBAX Oral Suspension caused gastrointestinal signs, including vomiting and soft and/or mucoid feces. At doses of 75 mg/kg/day, hypersalivation was observed. Male dogs treated with 75 mg/kg/day had reduced food consumption and mild weight loss. Glucosuria and lowered urine pH were also observed in dogs treated with orbifloxacin at 75 mg/kg/day. No clinical chemistry changes related to glucosuria and lower urine pH were observed, and the mechanism responsible for the glucosuria and lower pH in this group could not be determined. Following ten days of treatment with 75 mg/kg/day, one male dog developed hepatic perilobular necrosis and bile duct hyperplasia and inflammation which were associated with serum elevations in bilirubin and hepatic enzymes (ALP, ALT, AST, and GGT). The dog completed the study without clinical signs of illness. At necropsy, the liver had a tan discoloration and weighed less than the livers of other dogs in the group and control dogs. No treatment-related pathologic liver changes were noted in any other dogs treated with orbifloxacin during the study. Articular cartilage defects were observed in the head of the humerus in one male dog in the 3X dose group, and in the medial condyle of the distal femur in one male in the 5X dose group. Based on microscopic examination of these lesions, it was determined that both lesions were long-standing and were present prior to treatment with orbifloxacin.

Orbifloxacin Plasma Concentration Analyses:
The ratio of area under the curve (AUC) values estimated at steady state (AUC_{0-T}) versus after the first dose (AUC_{0-24}) was equal to or less than 1.30 across the four dosing groups, indicating that minimal drug accumulation occurred with a once daily dosing regimen. Blood levels achieved in males and females were similar, indicating the absence of gender effects. To determine the degree to which systemic exposure increased relative to administered dose, AUC_{0-24}, AUC_{0-T}, peak concentrations (C_{MAX}) and steady state trough concentrations (C_{MIN}) were compared across dosing groups. AUC_{0-24} and AUC_{0-T} increased in a less than dose-proportional manner. At doses of 1, 3, 5 and 10X the maximum recommended daily dose, the AUC values increased at a rate of 2.3, 3.3 and 4.3 X that observed at a dose of 7.5 mg/kg/day. Similar findings were obtained with C_{MAX}. To explore the potential bias attributable to failure to adequately capture C_{MAX}, C_{MIN} values were compared. Although the degree of nonlinearity was less than that assessed on the basis of AUC or C_{MAX} estimates, these results still suggest a less than dose-proportional increase in exposure, particularly with the 37.5 and 75 mg/kg dose-groups (Table 10). Because the proportion of AUC_{0-T} / AUC_{0-24} remained constant across all dosing groups, it is concluded that the apparent non-linear kinetics are attributable to dose related changes in the percent drug absorbed rather than to changes in drug clearance.

Table 10. Relative changes in AUC, C_{MAX1} and C_{MIN} (expressed relative to a 7.5 mg/kg dose). Note that T_{MAX1}, T_{MAXss} and C_{MAXss}/C_{MAX1} are estimated as means within each dose group and are not expressed relative to a 7.5 mg/kg dose (where C_{MAX1} and T_{MAX1} refer to values obtained at dose 1, and C_{MAXss} and $T_{MAX\ ss}$ refer to the values obtained at the final dosing interval).

Dose Group (mg/kg)	**AUC $_{0-24}$** Relative to 7.5 mg/kg dose	**AUC $_{0-T}$** Relative to 7.5 mg/kg dose	**C_{MAX1}** Relative to 7.5 mg/kg dose	**C_{MIN}** Relative to 7.5 mg/kg dose	**T_{MAX1} (hr)**	**T_{MAXss} (hr)**	**C_{MAXss}/ C_{MAX1}**	**AUC_{0-T}/ AUC_{0-24}**
7.5	1.00	1.00	1.00	1.00	2.6	2.7	1.12	1.18
22.5	2.06	2.54	1.90	3.2^{+}	3.1	2.4	1.73	1.33
37.5	2.82	3.82	3.78	4.3^{+}	3.8	2.8	1.13	l.78
75	4.23	4.30	4.58	6.8^{+}	2.7	3.2	1.00	1.29
%CV								
7.5	0.09	0.09	0.13					
22.5	0.31	0.18	0.32					
37.5	0.40	0.17	0.14					
75	0.18	0.45	0.14					

$^{+}$includes one subject that had unusually high steady state concentrations
C_{max} = peak observed drug concentration
T_{max} = time to C_{max}

Steady state C_{MIN} values represent an average of concentrations reported at hours zero and 24. Concentrations reported for the 7.5 mg/kg group are divided by that of

corresponding dosing group (X). AUC_{0-24} = AUC over the first dosing interval. $AUC_{0-\tau}$ = AUC over a single dosing interval at steady state. %CV = the variability associated with the corresponding parameters for each dosing group.

6. Conclusions: Dogs tolerated orally administered ORBAX Oral Suspension at doses up to 37.5 mg/kg/day. Test article-related white to yellow discoloration of the feces occurred in all treated groups and was considered to be due to the presence of test article-related material. Vomiting and soft and/or mucoid feces were observed only at doses of 37.5 and 75 mg/kg/day and may have been related to the large volume of oral liquid administered (1.25 -2.5 mL/kg) in order to deliver the required dose. Test article-related findings limited to the 75 mg/kg/day dose level included: salivation, decreased food consumption and body weight (males), and increased urine glucose. Also, one male dog treated with 75 mg/kg/day had elevated serum liver enzymes and bilirubin, decreased liver weight, and hepatic discoloration, which correlated microscopically with liver necrosis and bile duct hyperplasia. These changes were limited to this single dog and were considered to be a test article-related reaction.

VII. HUMAN FOOD SAFETY:

This drug is intended for use in cats and dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this application.

VIII. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ORBAX Oral Suspension:

Human Warnings are provided on the product label as follows: “For use in animals only. Keep out of the reach of children. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure.

The data submitted in support of this NADA were examined to ensure human user safety.

IX. 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 ORBAX (orbifloxacin) 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 *Staphylococcus aureus, Escherichia coli,* and *Pasteurella multocida.* The data demonstrate that ORBAX (orbifloxacin) Oral Suspension, when used according to the label, is safe and effective for the treatment of urinary tract infections (cystitis) in dogs caused by susceptible strains of *Staphylococcus pseudintermedius, Proteus mirabilis, Escherichia coli* and *Enterococcus faecalis.* The data demonstrate that ORBAX (orbifloxacin) Oral Suspension, when used according to the label, is safe and effective for the treatment of skin and soft tissue infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus pseudintermedius, Staphylococcus aureus,* coagulase positive staphylococci, *Pasteurella multocida, Proteus mirabilis, Pseudomonas* spp., *Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Citrobacter* spp., *Enterococcus faecalis,* β-hemolytic streptococci (Group G) and *Streptococcus equisimilis.*

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed in the diagnosis of bacterial infections in cats and dogs, treatment of these conditions, and monitoring for possible adverse reactions to the drug.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval.

C. Patent Information:

ORBAX Oral Suspension is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
6,514,492 B1	July 12, 2020

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

X. ATTACHMENTS:

Facsimile Labeling:
Package insert
Bottle
Carton