

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-081

B. Sponsor

Schering-Plough Animal Health Corporation
P.O. Box 529
Kenilworth, New Jersey 07033

C. Proprietary Name

Orbax™

D. Established Name

Orbifloxacin

E. Dosage Form

Tablet

ORBAX is available in 3 tablet strengths. The 2 larger sizes are scored to facilitate bisection.

Tablet Strength	Color
5.7 mg	Yellow
22.7 mg	Green
68.0 mg	Blue

F. Dispensing Status

Rx

G. Route of Administration and Frequency

Oral once daily.

H. Recommended Dose

The ORBAX (brand of orbifloxacin) Tablets dose is 2.5 mg/kg to 7.5 mg/kg of body weight administered orally once daily for up to a maximum of 30 days of therapy, if necessary. Treatment of skin and associated soft tissue infections should continue for two (2) to three (3) days beyond the cessation of clinical signs. Treatment of urinary cystitis should be for at least ten (10) consecutive days with diagnosis and treatment re-evaluation if improvement is not seen within the first five (5) days.

I. Indication

ORBAX (orbifloxacin) Tablets are indicated for the management of diseases in dogs associated with bacteria susceptible to orbifloxacin.

Clinical efficacy was established in skin and soft tissue infections (wounds and abscesses) and urinary tract infections (cystitis) associated with bacteria susceptible to orbifloxacin

II. EFFECTIVENESS

Data from the following studies demonstrate that ORBAX (brand of orbifloxacin) Tablets are effective for the treatment of canine dermal infections and urinary cystitis when administered orally at 2.5 mg/kg for up to ten (10) days. Clinical field studies were conducted in multiple geographic locations.

A. Dose Determination

Study Number : #1330C-61-V92-137-01

1. Type of Study:

Dose titration study of orbifloxacin tablets using an infected surgical wound model.

2. Investigators:

John N. Berg, DVM, Ph.D.
Richard E. Fish, DVM, Ph.D.
College of Veterinary Medicine
University of Missouri
Columbia, MO

3. General Design:

Purpose: To establish an effective dose of orbifloxacin tablets for the treatment of soft tissue infections in dogs using an infected surgical wound model.

Animals: Fifty-four (54) conditioned, 14.0 to 27.1 kg, male and female dogs of mixed breeding were used in the study.

Experimental Design: Fifty (50) dogs were randomly assigned into five (5) treatment groups (10 animals/group) as follows: 0 mg/kg (placebo); 0.625 mg/kg; 1.25 mg/kg; 2.5 mg/kg; 3.75 mg/kg. All treatments were administered orally once daily for five (5) consecutive days. Four (4) dogs were treated at 5 mg/kg for clinical comparison only, but were not included in the statistical comparison. *Escherichia coli* and *Klebsiella pneumoniae* isolated from naturally occurring canine wounds were used to infect the surgical sites (neck and abdomen).

Dosage Form: The orbifloxacin dosage form was a coated tablet containing 5.7, 22.7, or 68.0 mg of orbifloxacin.

Test Duration - Eleven (11) days

Pertinent Parameters Measured - These included bacteriological and hematological examinations, and general clinical appearance (food consumption/weight gain). In addition, all dogs were examined at necropsy.

4. Results:

Comparison of bacteria elimination rates at Day 9 of the wound model study established an effective dose of 2.5 mg/kg against *Escherichia coli*. Analysis of the dose response of Day 6 bacterial counts corroborates the choice of dose.

5. Adverse Drug Reactions:

No apparent drug-related adverse reactions were reported.

6. Conclusion:

Under the conditions of the study, ORBAX (brand of orbifloxacin) Tablets, administered once daily for five (5) consecutive days at a dose of 2.5 mg/kg body weight was effective in the treatment of surgical wounds infected with *Escherichia coli*.

B. Clinical Field Study - Canine Urinary Cystitis (Study No. : 1330C-61-V93-153)

1. Type of Study:

Multi-centered field study in dogs affected with urinary tract infections (cystitis).

2. Investigators:

Ten (10) licensed veterinarians in private clinics or referral hospitals in seven (7) different states served as investigators in the blinded positive-controlled clinical field study. Only seven (7) of the ten (10) veterinarians had a minimum of 2 bacteriologically confirmed cases per treatment group required for inclusion in the clinical efficacy analysis.

Ed. note: The following table has 5 columns.

Investigator	Location	# of Cases Enrolled	# of Cases Included in Clinical Efficacy Analysis	# of Cases Included in Bacteriology Analysis
Dr. S. Pearl	Schaumburg, IL	13	5	5
Dr. R. Yelland	San Leandro, CA	15	8	8
Dr. D. Kraniec	Urbana, IL	5	0	2
Drs. A. Shiro/R. Benjamin	Berkeley, CA	7	7	7
Dr. A. Pickering	Terre Haute, IN	13	6	6
Dr. J Fish	Jacksonville, FL	10	9	9
Dr. M. Van Ness	Houston, TX	19	9	9
Dr. L.D. Eckerman	Houston, TX	5	5	5
Dr. R. D. Smith	Kansas City, KS	1	0	0
Dr. R.L. Siffermen	Springfield, MS	8	0	3
Total		96	49	54

3. General Design:

Purpose: To demonstrate that orbifloxacin tablets administered at a dose of 2.5 mg/kg are safe and effective under clinical conditions for the treatment of urinary tract infections (cystitis) in dogs.

Animals: Thirty-one (31) breeds, including mixed breeds were represented in the 96 cases that were enrolled. Seventy-six (76) dogs were male and 18 were female (2 not reported). Ages ranged from one (1) year to fifteen (15) years and weights ranged from 4 to 110 lbs. Forty-nine (49) dogs qualified to be included in the clinical efficacy, ninety-one (91) in the safety, and fifty-four (54) in the bacteriological evaluations.

Diagnosis: Dogs to be entered in the study were affected by urinary tract infections (cystitis) characterized by the presence of clinical signs including, but not limited to dysuria, tenesmus, pollakiuria, hematuria, pain on abdominal palpation, thickening of the bladder wall, and incontinence. Failure to isolate

bacteria at zero (0) day was cause to exclude the dog from the clinical efficacy analysis.

Dosage Form: The orbifloxacin dosage form was a coated tablet containing 5.7, 22.7 or 68.0 mg. of orbifloxacin.

Control: The control product was an approved enrofloxacin oral tablet administered at 2.5 mg/kg twice daily for ten (10) consecutive days.

Doses: Orbifloxacin tablets were administered once daily at 2.5 mg/kg for ten (10) days.

Route of Administration: Oral

Test Duration: Fourteen (14) days.

Pertinent Parameters Measured: These included measurements of the clinical signs of urinary tract infections (cystitis) on days 0, 10, and 14 and an overall subjective assessment on day 14. A laboratory evaluation (urine bacteriological culture and susceptibility testing, urinalysis, hematology, and blood chemistry panel) was performed on days 0 and 14. Adverse drug reactions were recorded.

4. Results:

Urinalysis: Parameters improved following treatment with orbifloxacin.

Bacteriological: Orbifloxacin had an overall bacteria elimination rate of 100% (31/31) as outlined in the following table.

Ed. note: The following table has 4 columns.

Bacteria Elimination Rate

	Orbifloxacin		
Pathogen	# Eliminated	# Isolated on Day 0	% Eliminated
Enterococcus faecalis	3	3	100%
Escherichia coli	17	17	100%
Proteus mirabilis	6	6	100%
Staphylococcus intermedius	2	2	100%
Miscellaneous	3	3	100%
TOTAL	31	31	100%

All pathogens isolated from urine were susceptible in vitro to orbifloxacin.

Clinical Efficacy - Eighty-three percent (83%) (20/24) of the cases were evaluated as having an overall excellent clinical response to orbifloxacin therapy by the study investigators.

5. Adverse Drug Reactions:

No apparent drug-related adverse reactions were reported.

6. Conclusion:

Under the conditions of the study, ORBAX (brand of orbifloxacin) Tablets, administered once daily for ten (10) consecutive days at a dose of 2.5 mg/kg body weight were safe and effective in the treatment of canine urinary tract infections (cystitis).

C. Clinical Field Study - Canine Soft Tissue Infections (Study #1330C-61-V93-152)

1. Type of Study:

Multi-centered study in dogs affected by dermal infections (wounds and abscesses).

2. Investigators:

Thirteen licensed veterinarians in private clinics or referral hospitals located in ten states served as investigators in this blinded, positive-controlled clinical field study. Only eight (8) of the thirteen (13) veterinarians had a minimum of 2 bacteriologically confirmed cases per treatment group required for inclusion in the clinical efficacy analysis.

Ed. note: The following table has 4 columns.

Investigator	Location	# of Cases Enrolled	# of Cases Included in Clinical Efficacy Analysis
Dr. S. Pearl	Schaumburg, IL	10	8
Dr. R. Yelland	San Leandro, CA	13	6
Dr. T. Grieshaber	Indianapolis, IN	10	6
Dr. T. Schadler	Columbus, OH	12	9
Dr. A. Pickering	Terre Haute, IN	64	35
Dr. J. Empel	Atlanta, GA	2	0
Dr. B. Garrett	Dothan, AL	25	13
Dr. J. Fish	Jacksonville, FL	6	0
Dr. G. Atkinson	St Louis, MO	1	0
Dr. M. VanNess	Houston, TX	11	8
Dr. L.D. Eckerman	Houston, TX	1	0
Dr. R. D. Smith	Kansas City, KS	3	0
Dr. R.L. Sifferman	Springfield, MO	14	13
Total		172	98

3. General Design:

Purpose: To demonstrate that orbifloxacin tablets administered at a dose of 2.5 mg/kg are safe and effective under clinical conditions for the treatment of dermal infections (wounds and abscesses) in dogs.

Animals: Forty-four (44) breeds, as well as mixed breeds were represented in the 172 cases enrolled. Ninety-two (92) dogs were male and eighty (80) were female. Ages ranged from nine (9) months to sixteen (16) years and weights ranged from 5.6 to 122 lbs. Ninety-eight (98) of the enrolled dogs were evaluated for clinical efficacy

Diagnosis: Dogs to be included in this study were affected by wounds or abscesses limited to skin and soft tissue and were post-surgical or trauma related. Dogs were eliminated from the efficacy evaluation if the day 0 bacteriological culture was negative.

Dosage Form: The orbifloxacin dosage form was a coated tablet containing 5.7, 22.7, or 68.0 mg of orbifloxacin.

Controls: The control product was an approved enrofloxacin tablet administered at 2.5 mg/kg twice daily for 5 or 10 days.

Doses: Orbifloxacin tablets were administered once daily at 2.5 mg/kg for five (5) or ten (10) days.

Route of Administration: Oral

Test Duration: Six (6) or eleven (11) days - Treatment was initially administered for five (5) days (days 0-4). If treatment appeared to be successful, medication was terminated and the dog was re-examined on day 6. If the lesion was not healed on day 4, then treatment was administered for an additional five (5) days with the final examination on day 11.

Pertinent Parameters Measured: These included bacteriological culture and susceptibility testing, physical examination, lesion evaluation (clinical signs of inflammation), hematology and blood chemistry panel.

4. Results:

Wound healing: Wound healing characteristics were pivotal in establishing the efficacy of the product.

Day 5 – Healing

Of the 98 cases evaluated for efficacy, 41% (40/98) were noted as healed on Day 5. The results by treatment group are as follows.

Ed. note: The following table has 4 columns.

Wounds/Abscesses - Healed by Day 5

Treatment Group	Healed Day 5	Not Healed Day 5	No. of Evaluated Cases
Orbifloxacin	24 (43%)	32 (57%)	56
Enrofloxacin	16 (38%)	26 (62%)	42

Day 11 – Healing

At Day 11, 89% (87/98) of the cases were considered to be healed. The results by treatment group are as follows.

Ed. note: The following table has 4 columns.

Wounds/Abscesses - Healed by Day 11

Treatment Group	Healed Day 5	Not Healed Day 5	No. of Evaluated Cases
Orbifloxacin	49 (88%)	7 (12%)	56
Enrofloxacin	38 (38%)	4 (10%)	42

Clinical Signs: Clinical signs noted in both orbifloxacin and enrofloxacin treated groups, including those usually associated with inflammation (heat, redness, swelling, and pain) diminished consistent with the healing process. The

orbifloxacin group had changes from day 0 to day 11 that were generally statistically significant ($p < 0.0001$). There were no significant differences in body temperatures (rectal) which were normal or only slightly elevated at Day 0.

Hematology and Blood Chemistry: There were no changes in either hematology or blood chemistry parameters for either treatment group.

Bacteriological: A total of 216 organisms were isolated on pre-treatment culture from the 98 cases evaluated for efficacy. Of these, 120 were subjected to orbifloxacin and 96 to enrofloxacin tablet medication. Both drugs performed well with an overall day 11 elimination rate of 96% (115/120) for orbifloxacin and 98% (94/96) for enrofloxacin. Staphylococcus intermedius was the most common pathogen isolated. Orbifloxacin treatment eliminated 100% (21/21) while enrofloxacin therapy eliminated 95% (18/19). In vitro susceptibility testing (MIC) corroborated the effectiveness of orbifloxacin against the isolated bacteria.

5. Adverse Drug Reactions:

No apparent drug-related adverse reactions were reported.

6. Conclusion:

Under the conditions of the study, ORBAX (brand of orbifloxacin) tablets administered once daily for five (5) or ten (10) consecutive days at a dose of 2.5 mg/kg body weight were a safe and effective treatment of dermal infections (wounds or abscesses) in dogs.

D. Canine Pharmacokinetics

Study Report Number: P-6042

1. Type of Study:

Pharmacokinetic study conducted with administration of a single intravenous bolus or oral (tablet) 2.5 mg/kg dose to male and female dogs.

2. Study Director:

Craig R. Mahon, B.S.
Battelle Laboratories
Columbus, OH

3. General Design:

Purpose: The purpose of this study was to determine the pharmacokinetics of orbifloxacin in dogs following administration of a single intravenous bolus or single oral tablet at a dose of 2.5 mg/kg.

Animal: Twelve Beagle Dogs (6 male, 6 female) approximately sixteen (16) to seventeen (17) months of age weighing 10.6 to 14.5 kg (males) and 9.3 to 13.0 kg (females) were used in this study.

Dogs were randomly assigned to groups by weight and sex in a two period, two sequence crossover design. In the first period, three (3) dogs/sex were administered a single oral dose of orbifloxacin tablets at 2.5 mg/kg of body

weight and another group of three (3) dogs/sex were administered a single intravenous bolus of orbifloxacin at a dose of 2.5 mg/kg of body weight. After the first period of the study, a washout period of fourteen (14) days was allowed before the animals were crossed over in the second period and treated by the other route of administration.

Dosage Forms: Orbifloxacin 5.7, 22.7, and 68.0 mg tablets. Orbifloxacin injectable solution, 10 mg/mL.

Routes of Administration: Oral and intravenous.

Pertinent Parameters Measured: Plasma and urine orbifloxacin concentrations were determined by validated high performance liquid chromatography (HPLC) methods.

4. Results:

The following tables contain a summary of the pharmacokinetic results following intravenous (IV) and oral administration:

Table 1. Mean pharmacokinetic parameters estimated in 12 dogs after IV administration of orbifloxacin at 2.5 mg / kg

Pharmacokinetic parameter	Estimate (SD)
Total body clearance, mL/min/kg	2.92 ± 0.18
Volume of distribution at steady state, Vss (L/kg)	1.2 ± 0.2
AUC0-infinity (ugh/mL)	14.32 ± 0.93
Terminal plasma elimination half-life, t1/2 (hrs)	14.32 ± 0.93

Table 2. Mean pharmacokinetic parameters estimated in 12 dogs after oral administration of orbifloxacin at 2.5 mg / k

Pharmacokinetic parameter	Estimate (SD)
Total body clearance/F, mL/min/kg	3.02 ± 0.20
Maximum concentration, Cmax (ug/mL)	2.33 ± 0.28
Time of maximum concentration, Tmax (minutes)	46 ± 27
AUC0-infinity (ugh/mL)	14.26 ± 1.4
Terminal plasma half-life, t1/2 (hrs)	5.6 ± 1.1

5. Adverse Drug Reactions:

No apparent drug-related adverse reactions were reported.

6. Conclusions:

Orbifloxacin is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. The absolute bioavailability, F, of a 2.5 mg/kg oral dose is approximately 97%. Peak plasma concentrations are usually attained within one hour of administration. The relatively large volume of distribution at steady-state, Vdss, is indicative of a widespread distribution and penetration into body tissues. Approximately 40% of an oral dose was excreted by the kidneys into the urine unchanged in animals with normal renal function within 24 hours of administration. Based on the plasma elimination half-life and the dosing interval, negligible drug accumulation is expected with multiple dosing. There were no apparent gender related differences in pharmacokinetic parameters.

III. TARGET ANIMAL SAFETY

A. Target Animal Safety

Study Report Number: 93504

1. Type of Study:

This was a target animal safety study conducted in beagle dogs administered orbifloxacin tablets daily at 1X (7.5 mg/kg), 3X (22.5 mg/kg), and 5X (37.5 mg/kg) for a duration of 30 days.

2. Study Director:

Craig R. Mahon, B.S.
Battelle Laboratories
Columbus, Ohio

3. General Design:

Purpose: The study conducted in compliance with the Food and Drug Administration's Good Laboratory Practice Regulations was designed to evaluate the safety and determine the toxicological effects of orbifloxacin when administered orally to beagle dogs. Potential target organs and tissues were to be identified and systemic drug absorption determined.

Animals: Thirty-two (32) young adult (approximately 15-16 month old) beagle dogs (16 males and 16 females) weighing 9.43 - 14.31 kg of body weight at study initiation were randomly allotted into four (4) groups consisting of four (4) males and four (4) females in each of the control, 1X, 3X, and 5X dose groups.

Dosage Form: Orbifloxacin 5.7, 22.7, and 68.0 mg coated tablets.

Control: Dogs were "mock" dosed; that is, they were manipulated in the same way as the orbifloxacin treated dogs but were not administered the test article.

Route of Administration: Oral

Dose: 0 (untreated control group), 7.5, 22.5, or 37.5 mg/kg/day for 30 consecutive days.

Test Duration: 30 days.

Pertinent Parameters Measured: Survival, clinical observations, physical examinations, food consumption and body weight, electrocardiograms (ECGs), ophthalmic examinations, clinical, gross, and histo-, pathology and plasma drug concentration analyses.

4. Results:

Other than discoloration of feces in the 3X and 5X dose groups due to the tablet coating, there were no apparent drug-related adverse reactions reported.

In a review of the plasma drug concentrations taken after the last dose (Day 30), it is apparent that the absorption of orally administered orbifloxacin increases proportionately with dose (exhibits linear pharmacokinetics) up to 37.5 mg/kg when given daily for 30 days. In comparison with drug plasma levels measured in the pharmacokinetic study, drug accumulation was not observed.

5. Conclusions:

Results of this study support the conclusion that oral administration of orbifloxacin at the maximum intended clinical dose of 7.5 mg/kg/day for a maximum duration of thirty (30) days produces no systemic effects in young adult (15-16 month) beagle dogs.

B. Effect of orbifloxacin on the articular cartilage of young dogs

Study # 1330C-61-V93-144

A specially designed exploratory study was conducted to make a preliminary determination of the potential of orbifloxacin to induce an arthropathy in young, rapidly growing dogs. The potential of fluoroquinolones to induce an arthropathy in the weight-bearing joints of juvenile animals is well-documented in the literature. The dog is reported to be particularly sensitive to this phenomenon.

1. Type of Study:

This was a 30 day study in beagle dogs administered either orbifloxacin or placebo tablets.

2. Investigators:

Study Director:
Fred E. Lowrey, DVM, MS
Lancaster Animal Services
Lincoln, Nebraska

3. General Design:

Purpose: This study was conducted to determine, on a preliminary basis, if orbifloxacin when administered orally has the potential to induce arthropathy in young, rapidly growing beagle dogs.

Animals: Twenty (20) 8-10 week old, 4-8 lb beagle dogs (10 male and 10 female) were allotted among three treatment groups. (See Study Design)

Dosage Form: Orbifloxacin 68.0 mg tablets.

Control: A lactose placebo tablet was used.

Route of Administration: Oral

Dose: 0 (placebo control group), 12.5 or 25 mg/kg body weight/day for 30 days (dogs missed one dose during the study and therefore only received 29 total doses).

Design

Treatment	8-10 week old beagle
Placebo (Lactose Tablet)	2 male, 2 female
12.5 mg / kg Once Daily Orbifloxacin Tablets	4 male, 4 female
25.0 mg / kg Once Daily Orbifloxacin Tablets	4 male, 4 female

Pertinent Parameters Measured: Clinical signs such as arthralgia, joint swelling, and gross and histo-, pathological examination of selected joints.

4. Results:

Clinical signs consistent with fluoroquinolone-induced arthralgia (e.g., limping and carpal flexion) were noted in six of eight dogs in the 12.5 mg/kg of body weight group and in six of eight in the 25mg/kg of body weight group.

Gross lesions were not seen in any dog in the placebo or lower (12.5 mg/kg) dose group. Five of the eight high dose dogs (25.0 mg/kg) had lesions visible in the articular cartilage of one or more joints. Microscopic lesions consistent with fluoroquinolone induced arthropathy were seen in all high dose dogs and 1 dog in the lower dosage group.

5. Conclusion:

Under the conditions of the study, ORBAX (brand of orbifloxacin) Tablets, are not safe to use in young growing beagle dogs.

IV. HUMAN FOOD SAFETY

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

V. AGENCY CONCLUSIONS

The data submitted in support of this original NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 514.111 of the implementing regulations. The data demonstrate that ORBAX (orbifloxacin) Tablets, when used under the labeled conditions of use, are safe and effective.

Orbifloxacin is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis is required for safe use and treatment success.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for 5 years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

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.