

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-081

B. Sponsor

Schering-Plough Animal Health
P.O. Box 529
Kenilworth, NJ 07033

C. Proprietary Name

Orbax™ tablets

D. Established Name

orbifloxacin tablets

E. Dosage Form

Tablet

F. Dispensing Status

Rx

G. Indication

Orbax tablets are indicated for the management of diseases in dogs and cats associated with bacteria susceptible to orbifloxacin.

H. Effect of Supplement

The supplement to NADA 141-081, for dogs, provides for revisions to 21 CFR 520.1616 and the use of Orbax (orbifloxacin) tablets in cats as indicated below. §520.1616 *Orbifloxacin tablets*.

(d) *Conditions of use. (1) Dogs and cats.*

II. EFFECTIVENESS

A. Dosage Rationale and additional label information

The following pharmacokinetic indices determined from data collected in studies of cats and dogs were used to rationalize the dosage and to support label information. The dose was justified by the similarity of pharmacokinetic indices determined from serum profiles in dogs (see FOI summary, NADA 141-081, dated April 22, 1997) and cats as indicated in Table 1. The similarity between the C_{max} and AUC (two indices relative to fluoroquinolone efficacy) allow for the choice of dose.

Drug accumulation was expected to be negligible based on a drug accumulation index (R) of 1.03, estimated from a single dose study, (study number: P-6063). This

was confirmed by orbifloxacin plasma concentration data collected after thirty (30) days of administration in the target animal safety study for cats (study number 94503). The negligible drug accumulation coupled with the lack of adverse responses evident in the clinical field and target animal safety studies supports a maximum thirty (30) day duration of therapy.

1. *Feline Pharmacokinetics:*

a. *Title:*

Study Number: P-6063, Pharmacokinetics of orbifloxacin following administration of either a single intravenous or oral (ORBAX tablet) 2.5 mg/kg dose to male and female cats.

b. *Investigators:*

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Anup Zutshi, Ph.D.
Steven W. Graves, B.S.
Michael E. Placke, Ph.D.
Batelle
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c. *Purpose:*

The purpose of this study was to investigate the pharmacokinetics and determine the bioavailability of orbifloxacin administered intravenously and ORBAX administered orally at a single 2.5 mg/kg dose in cats.

d. *Materials and methods*

- i. *Animals:* Twelve adult domestic short-hair cats (6 male and 6 female), approximately 13 to 16 months of age and weighing 4.6 to 5.3 kg (males) and 2.8 to 3.6 kg (females) at initiation of treatment were used in this study.
- ii. *Study design:* A two-period, cross-over design, orthogonal to treatment with a 14-day washout period was used. The dose for both routes and formulations was 2.5 mg/kg of body weight.

e. *Results:*

See Table 1

Table 1. Summary of group mean pharmacokinetic parameters in cats and dogs after oral administration of ORBAX tablets at 2.5 mg/kg of body weight. The indices determined for cats are dose normalized to 2.5 mg/kg.

Pharmacokinetic index	Species	
	Dog - Estimate (SD)	Cat – Estimate (SD)
Total body clearance/F, [mL/min/kg]	3.02 ± 0.20	3.98 ± .79
Concentration maximum [C _{max} (ug/mL)]	2.33 ± 0.28	2.06 ± .60
Time of maximum concentration [T _{max} (minutes)]	46 ± 27	60 ± .27
Area under the curve [AUC _{0-∞} (ug·h/mL)]	14.26 ± 1.4	10.82 ± .2.6
Terminal plasma elimination half-life [t _{1/2} (hrs)]	5.6 ± 0.1.1	5.52 ± .2.66
Drug accumulation index (R)	1.04	1.03
Bioavailability (F)	Essentially 100%	Essentially 100%

B. Clinical field trial: Dermal infections (wounds and abscesses) in cats, study number 1350C-61-V94-201

1. *Purpose:*

The purpose of this study was to demonstrate that ORBAX tablets administered orally at 2.5 mg/kg is safe and effective under clinical conditions for the management of skin and associated soft-tissue infections (wounds and abscesses) in cats.

2. *Design:*

This was a multi-center study evaluating cats affected by skin and associated soft-tissue infections (wounds and abscesses) that required systemic antibiotic therapy.

3. *Materials and methods:*

a. *Entrance criteria:*

Demonstration of dermal infection with culture positive lesions. The wound was to be debrided.

b. *Investigators:*

Seven licensed veterinarians in private clinical practice, or referral hospitals, located in 6 states served as investigators in this blinded, positive controlled,

clinical field study. Of these, 5 produced a sufficient number of cases to be included in the clinical efficacy analysis.

c. *Animals:*

A total of 175 cases were enrolled in the study. Of these, 149 (85%) were domestic-long-hair or short-hair cats. Due to negative bacteriologic cultures, protocol violations and insufficient case load per investigator, 91 cases were evaluated for clinical efficacy (n = 44 in the ORBAX group, n = 47 in the BAYTRIL™ (enrofloxacin) tablet treated group. Ages ranged from 4 months to 18 years and weights from 2 lb to 22 lb. One hundred thirty (130) cats were male (23 neutered) and 45 were female (14 spayed).

d. *Assignment:*

Random assignment to treatment consisting of ORBAX (2.5 mg/kg/day, oral, SID, 5 or 10 days) or BAYTRIL™ (2.5 mg/kg/day, oral, BID, 5 or 10 days). Treatment was initially administered for five (5) days. If the lesion appeared to be healed at the Day 5 examination, treatment was discontinued. Otherwise, treatment was continued for an additional five days with relapse and overall success assessed by the investigator on Day 11.

4. *Results:*

Table 2 indicates the investigators, number of animals enrolled and analyzed. Table 3 indicates the lesion types as enrolled.

Table 2. Investigators, location, number of cases enrolled and included in study number 1350C-61-V94-201 designed to evaluate the effectiveness of ORBAX™ in cats. NS indicates that the number of animals was not sufficient to be included in the analysis.			
Investigator	Location	Number Enrolled	Number analyzed
Dr. S. Pear.	Schaumburg, IL	7	7
Dr. R. Yelland	San Leandro, CA	20	43
Dr. A. Pickering	Terre Haute, IN	33	31
Dr. J. Empel	Atlanta, GA	2	NS
Drs. D. Gahring & B. Persky	San Diego, CA	11	NS
Dr. Ben Garrett	Dothan, AL	12	8
Dr. R. Sifferman	Springfield, MO	67	35
Total		175	91

Table 3. Lesion types in cats enrolled in study number 1350C-61-V94-201 designed to evaluate the effectiveness of ORBAX™ in cats.	
Lesion Type	Number
Closed abscesses	45
Open abscesses	74
Closed wounds	3
Open wounds	53
Total	175

Both treatments eliminated 100% of the most commonly occurring bacteria which included: *Pasteurella multocida*, *Staphylococcus intermedius*, *Enterococcus* spp., *E. coli*, *Enterobacter* spp., and Group G. 8 Hemolytic streptococci.

The overall assessment is presented in Table 4. Both compounds were effective in reducing erythema, warmth, swelling, pain, discharge/aspirate volume, and pyrexia. An exact 95% confidence interval for the healing rate in the ORBAX-treated cats is 72.6% to 94.8%. An exact 95% confidence interval for the healing rate in the BAYTRIL™ treated cats is 79.6% to 97.6%. THE STUDY WAS DESIGNED TO DETECT CHANGES FROM BASELINE BUT WAS NOT DESIGNED WITH SUFFICIENT POWER TO DETECT DIFFERENCES BETWEEN THE TWO TREATMENTS.

Table 4. Number, percentage and confidence intervals for treatment success of wounds/abscesses healed by Day 11 in study number 1350C-61-V94-201 designed to evaluate the effectiveness of ORBAX™ in cats.			
Treatment group	Treatment success	Confidence interval for treatment success	No. of cases evaluated
ORBAX™	38 (86%)	72.6% to 94.8%	44
BAYTRIL™	43 (91%)	79.6% to 97.6%	47

A total of 169 cases were evaluated for safety. One cat in the ORBAX treated group (1/82) developed a mild degree of vomition on the third day of treatment. Treatment was discontinued. It could not be determined if the adverse event was drug related.

C. Conclusion:

Under the conditions of this 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 was safe and effective in the treatment of skin and soft tissue infections (wounds or abscesses) in cats.

III. TARGET ANIMAL SAFETY

A. Title:

Study Number 94503, Target animal safety study of SCH 51854 (orbifloxacin) tablets in cats.

1. Purpose:

The study was designed to evaluate the safety of ORBAX when administered orally to domestic short-hair cats.

2. Design:

This was a 30-day study in domestic short-hair cats administered ORBAX tablets at 1, 3, and 5 times the highest recommended dose.

3. Materials and methods

a. Investigators

Craig R. Mahon, B. S. - Study Director
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b. *Animals*: Thirty-two young adult (13 to 17 months old) domestic short-hair cats (16 male and 16 female) weighing 4.69 to 4.79 kg (mean of males) and 3.00 to 3.16 kg (mean of females) at study initiation were randomly allotted into 4 groups consisting of 4 males and 4 females in each of the control, low-, mid- and high-dose groups.

c. *Dosage* ORBAX tablets (5.7, 22.7 and 68.0 mg-coated tablets) were administered at 1, 3, and 5 times the highest recommended dose (7.5 mg/kg) for 30 days.

d. *Pertinent Parameters Measured*: Survival, general clinical condition, clinical and physical examination, body weight, food consumption, organ weight, electrocardiogram (ECG), ophthalmic examination, clinical pathology, and gross and histopathology information.

4. Results

a. Clinical Observations:

Higher doses (22.5 and 37.5 mg/kg/day of orbifloxacin) caused mild gastrointestinal effects (soft feces) in both males and females. This was probably associated with alteration of intestinal microorganism populations by exaggerated doses of orbifloxacin. Slight, but significantly decreased weight gains accompanied by slightly decreased feed consumption were noted in female cats that received 37.5 mg/kg of orbifloxacin. Rectal temperature,

heart rate and respiratory rate were unaffected by treatment. No adverse responses were seen on clinical, or post-mortem pathologic examination.

5. *Conclusions:*

Results of this study support the conclusion that oral administration of ORBAX tablets at the maximum intended clinical dose of 7.5 mg/kg/day for thirty (30) days produces no adverse effects in young adult (13 to 17 month) domestic short-hair cats. Mild gastrointestinal effects were noted at higher doses (22.5 to 37.5 mg/kg). There were only minimal toxic effects at doses up to five (5) times (37.5 mg/kg) the maximum clinical dose when administered for thirty (30) days.

B. Title:

Target animal safety study of SCH 51854 (Orbifloxacin) tablets in kittens, Report # P-6400.

1. *Purpose:*

The purpose of the study was to evaluate the safety of ORBAX when administered orally to domestic short-hair kittens.

2. *Materials and methods:*

a. *Investigators:*

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b. *Animals:*

Thirty-two, young (12-week-old) domestic short-hair kittens (16 male and 16 female) weighing 874 to 1172 g (males) and 689 to 1204 g (females) at study initiation were randomly allotted into 4 groups consisting of 4 males and 4 females in each of the control, low-, mid- and high-dose groups.

c. *Dosage:*

ORBAX 5.7 mg coated tablets were administered at Zero (0), 3.0 to 7.9, 7.0 to 14.9, and 9.2 to 25.3 mg/kg/day for 31 or 32 consecutive days (1, 2 or 3 tablets).

d. *Pertinent parameters measured:*

Survival, general clinical observations, physical examinations, food consumption and body weight, clinical pathology, gross pathology and histopathology of the articular cartilage.

e. *Observations:*

Minor adverse clinical findings were noted. Limited, transient occurrence of soft stool occurred in all groups treated with ORBAX. These generally occurred on days 1 or 2. Rectal temperature, heart and respiratory rates, food consumption and body weight were unaffected by treatment. No adverse responses were seen on clinical, or post-mortem pathologic examination.

f. *Conclusions:*

Results of this study support the conclusion that oral administration of ORBAX at the maximum intended clinical dose of 7.5 mg/kg/day for 31 to 32 days is not associated with adverse systemic effects in domestic short-hair kittens.

IV. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and Part 514 of the implementing regulations (Title 21), and demonstrate that Orbax (orbifloxacin) Tablets are safe and effective when used according to the approved conditions of use.

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

According to the Center's supplemental approval policy 21 CFR 514.106(b)(2)(vii) ["Addition of a new species"] this is a Category II change.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non-food animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the added species for which the supplement was approved.

FDA has carefully considered the potential environmental effects of this action and has concluded that the action is categorically excluded from the need to provide an environmental assessment (see 62 FR 40570 § 40596, July 29, 1997), since the drug is intended for use in nonfood animals.

U.S. Patent No. 4,795,751 applies to Orbax Tablets and expires on October 28, 2006.

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.