

Date of Approval: MAR 3 2006

FREEDOM OF INFORMATION SUMMARY

NADA 141-081

ORBAX Tablets

orbifloxacin

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

Sponsored by:

Schering-Plough Animal Health Corp.
556 Morris Ave.
Summit, NJ 07901

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1. GENERAL INFORMATION:

- a. File Number: NADA 141-081
- b. Sponsor: Schering-Plough Animal Health Corp.
556 Morris Ave.
Summit, NJ 07901
- Drug Labeler Code: 000061
- c. Established Name: Orbifloxacin
- d. Proprietary Name: ORBAX Tablets
- e. Dosage Form: Tablet
- f. How Supplied: The product is available in the following presentations:
- 5.7 mg: yellow tablets in bottles of 250
- 22.7 mg: green single-scored (E-Z Break) tablets in bottles of 250
- 68 mg: blue single-scored (E-Z Break) tablets in bottles of 100
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Three tablet sizes: 5.7 mg, 22.7 mg, and 68 mg
- i. Route of Administration: Oral
- j. Species/Class: Canine and feline
- k. Recommended Dosage: 2.5 to 7.5 mg/kg of bodyweight administered once daily.

For the treatment of skin and associated soft tissue infections, ORBAX Tablets should be given for two (2) to three (3) days beyond the cessation of clinical signs to a maximum of 30 days. For the treatment of urinary tract infections, ORBAX Tablets should be administered for at least ten (10) consecutive days.

- l. Pharmacological Category: Antimicrobial
- m. Indications: ORBAX Tablets (orbifloxacin) are indicated for the management of diseases in dogs and cats associated with bacteria susceptible to orbifloxacin.
- n. Effect of Supplement: The supplement adds post-approval adverse drug experience information and fluoroquinolone class statements regarding retinal toxicity in cats.

2. EFFECTIVENESS:

- a. Dosage Characterization:* New information was not required for this supplement.
- b. Substantial Evidence:* New information was not required for this supplement.

3. TARGET ANIMAL SAFETY:

Target Animal Safety was demonstrated for the original approval for the use of ORBAX Tablets in the dog approved on April 22, 1997 and for the supplemental approval for the use of ORBAX Tablets in the cat approved September 18, 1997.

The current changes to product labeling are based on post-approval drug experience report monitoring:

Warnings: Human warnings were changed to read "Warnings" and the following sentence was added under the Warnings section: "Do not exceed 7.5 mg/kg body weight per day in cats."

Precautions: The following statements were added to the Precautions section: "The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats." The last statement in the Precautions section was changed from "Safety in breeding or pregnant dogs and cats has not been established" to read "The safety of orbifloxacin in animals that are used for breeding or that are pregnant and/or lactating has not been demonstrated."

At the end of the Adverse Reactions section, a post-approval section was added. This section is entitled "Post Approval Experience" and contains the following language: "The following adverse reactions, although rare, are based upon voluntary post-approval reporting:

- Hypersensitivity: facial edema, anaphylaxis/anaphylactoid reactions
- Neurologic: seizures, ataxia
- Behavioral: depression, lethargy
- Gastrointestinal: vomiting, anorexia"

4. *HUMAN SAFETY:*

This drug is intended for use in dogs and cats, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

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

5. *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 of the implementing regulations. The data demonstrate that ORBAX Tablets when used under the labeled conditions of use is safe and effective. Clinical effectiveness was established in skin and soft tissue infections (wounds and abscesses) in the dog and cat and urinary tract infections (cystitis) in the dog.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and treat bacterial infections in dogs and cats.

This approval for ORBAX Tablets does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug.

Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

6. *ATTACHMENTS:*

Facsimile labeling is attached as indicated below:

Package insert

NADA #141-081, Approved by FDA.

F-13335658

ORBAX® Tablets (orbifloxacin)

For Oral Use in Dogs and Cats Only

81-497245

Federal law prohibits the extralabel use of this drug in food-producing animals.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Orbifloxacin is a synthetic broad-spectrum antibacterial agent from the class of fluoroquinolone carboxylic acid derivatives. Orbifloxacin is the international nonproprietary name for 1-cyclopropyl-5,6,8-trifluoro-1,4-dihydro-7-(*cis*-3,5-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid. The chemical formula for orbifloxacin is $C_{19}H_{20}F_3N_3O_3$ and its molecular weight is 395.38.

The compound is slightly soluble in water; however, solubility increases in both acidic and alkaline conditions. The compound has two dissociation constants (pKa's): 5.95 and 9.01.

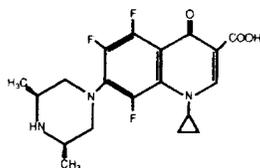


FIGURE 1. Chemical structure of orbifloxacin.

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

EFFICACY CONFIRMATION: Clinical efficacy was established in skin and soft tissue infections (wounds and abscesses) in the dog and cat, and urinary tract infections (cystitis) in the dog, associated with bacteria susceptible to orbifloxacin. Specific bacterial pathogens isolated in clinical field trials are listed in the **MICROBIOLOGY** section.

DOSEAGE AND ADMINISTRATION: For routine outpatient treatment of infection caused by a susceptible organism, in an otherwise healthy dog or cat, the dose of ORBAX® (orbifloxacin) Tablets is 2.5 to 7.5 mg/kg of body weight administered once daily. (See **DRUG INTERACTIONS** and **TARGET ANIMAL SAFETY**.) The determination of dosage for any particular patient must take into consideration such factors as the severity and nature of the infection, the susceptibility of the causative organism, and the integrity of the patient's host-defense mechanisms. Antibiotic susceptibility of the pathogenic organism(s) should be determined prior to use of this preparation. Therapy with ORBAX® (orbifloxacin) Tablets may be initiated before results of these tests are known. Once results become available, continue with appropriate therapy.

For the treatment of skin and associated soft tissue infections, ORBAX® Tablets should be given for two (2) to three (3) days beyond the cessation of clinical signs to a maximum of 30 days. For the treatment of urinary tract infections, ORBAX® Tablets should be administered for at least 10 consecutive days. If no improvement is seen within five (5) days, the diagnosis should be re-evaluated and a different course of therapy considered.

To administer a total daily dose of 2.5 mg/kg, ORBAX® Tablets may be dispensed as indicated in Table 1.

Table 1: Dose Table for ORBAX® Tablets
(2.5 mg/kg total daily dose)
WEIGHT OF DOG/CAT (lbs)

Weight (lbs)	5	10	20	30	40	50	60	90	120
No. of 5.7 mg tablets	1	2							
No. of 22.7 mg tablets	½	1	1½	2	2½				
No. of 68 mg tablets		½				1	1½	2	

CLINICAL PHARMACOLOGY: Pharmacokinetics in healthy adult beagle dogs and healthy adult cats: In fasted animals, orbifloxacin is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. Absorption of orally administered orbifloxacin increases proportionately with dose (exhibits linear pharmacokinetics) up to 37.5 mg/kg when given daily for 30 days. The absolute bioavailability (F) of an oral

dose is approximately 100%. Peak plasma concentrations are usually attained within 1 hour of administration. The effects of concomitant feeding on the absorption of orbifloxacin has not been studied. Divalent cations are generally known to diminish the absorption of fluoroquinolones. (See **DRUG INTERACTIONS**.)

The relatively large volume of distribution at steady state (V_{ss}) is indicative of a widespread distribution and penetration into body tissues. Within 24 hours of administration, approximately 40% of an oral dose was excreted into the urine unchanged in dogs with normal renal function. This supports the efficacy of orbifloxacin in the treatment of urinary tract infections. Based on the plasma elimination half-life and the dosing interval, negligible drug accumulation is expected with multiple dosing.

Pharmacokinetic parameters estimated in a randomized two-period, two-sequence crossover study using single intravenous and oral doses are summarized in Tables 2 and 3 and Figures 2 and 3.

Table 2: Mean Pharmacokinetic Parameters Estimated in 12 Adult Beagle Dogs and 12 Adult Cats After a Single IV Bolus of Orbifloxacin at 2.5 mg/kg

Pharmacokinetic Parameter	Dog Estimate (SD)	Cat Estimate (SD)
Total body clearance, mL/min/kg	2.9 ± 0.2	4.09 ± 0.7
Volume of distribution at steady state, V_{ss} (L/kg)	1.2 ± 0.2	1.3 ± 0.13
$AUC_{0-\infty}$ (μ g·h/mL)	14.3 ± 0.9	10.6 ± 2.4
Terminal plasma elimination half-life, $t_{1/2}$ (hrs)	5.4 ± 1.1	4.5 ± 1.8

Table 3: Mean Pharmacokinetic Parameters Estimated in 12 Adult Beagle Dogs and 12 Adult Cats After a Single Oral Dose of Orbifloxacin at 2.5 mg/kg

Pharmacokinetic Parameter	Dog Estimate (SD)	Cat Estimate (SD)
Total body clearance/F, mL/min/kg	3.0 ± 0.2	3.98 ± 0.8
Maximum concentration, C_{max} (μ g/mL)	2.3 ± 0.3	2.06 ± 0.6
Time of maximum concentration, T_{max} (minutes)	46 ± 27	60 ± 27
$AUC_{0-\infty}$ (μ g·h/mL)	14.3 ± 1.4	10.82 ± 2.6
Terminal plasma elimination half-life, $t_{1/2}$ (hrs)	5.6 ± 1.1	5.52 ± 2.66

Plasma Concentration of Orbifloxacin vs. Time in Dogs

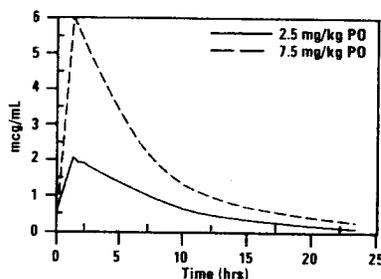


Figure 2. Mean plasma concentration of orbifloxacin vs. time in dogs (2.5 mg/kg = observed values, 7.5 mg/kg = extrapolated values).

Plasma Concentration of Orbifloxacin vs. Time in Cats

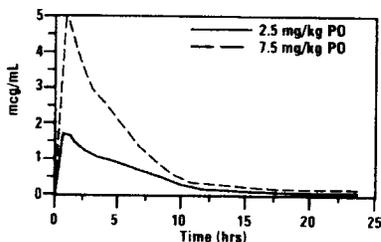


Figure 3. Mean plasma concentration of orbifloxacin vs. time in cats (2.5 mg/kg = normalized from an actual mean dose of 3.32 mg/kg; 7.5 mg/kg = extrapolated values).

MICROBIOLOGY: Orbifloxacin is bactericidal against a wide range of gram-negative and gram-positive organisms and exerts its antibacterial effect through interference with the bacterial enzyme DNA gyrase which is needed for the maintenance and synthesis of bacterial DNA. The minimum inhibitory concentrations (MICs) of pathogens isolated in multicentered clinical field trials performed in the United States were determined using National Committee for Clinical Laboratory Standards (NCCLS), and are shown in Tables 4, 5, and 6.

Table 4: MIC Values* (µg/mL) of Orbifloxacin Against Urinary Pathogens Isolated Between 1994 and 1996 From Clinical Infections in Dogs

Bacteria Name	Number of Isolates	MIC ₅₀	MIC ₉₀	MIC Range
<i>Staphylococcus intermedius</i>	5	**	**	0.0975 - 0.39
<i>Proteus mirabilis</i>	19	0.78	1.56	0.048 - 1.56
<i>Escherichia coli</i>	35	0.0975	0.39	0.024 - >25
<i>Enterococcus faecalis</i>	5	**	**	0.003 - 3.12

*The correlation between the *in vitro* susceptibility data (MIC Values) and clinical response has not been determined.

**There were an insufficient number of isolates to calculate the MIC₅₀ or MIC₉₀.

Table 5: MIC Values* (µg/mL) of Orbifloxacin Against Dermal Pathogens Isolated Between 1994 and 1996 From Clinical Infections of Dogs

Bacteria Name	Number of Isolates	MIC ₅₀	MIC ₉₀	MIC Range
<i>Staphylococcus intermedius</i>	51	0.195	0.39	0.003 - 1.56
<i>Staphylococcus aureus</i>	8	**	**	0.195 - >25
Coagulase +ve staphylococci	59	0.195	0.39	0.003 - >25
<i>Pasteurella multocida</i>	5	**	0	0.003 - 0.78
<i>Proteus mirabilis</i>	7	**	**	0.39 - 1.56
<i>Pseudomonas aeruginosa</i>	14	3.125	12.5	0.39 - >25
<i>Pseudomonas spp.</i>	18	3.125	12.5	0.02 - >25
<i>Klebsiella pneumoniae</i>	9	**	**	0.0975 - 0.195
<i>Escherichia coli</i>	28	0.0975	0.39	0.012 - 6.25
<i>Enterobacter spp.</i>	24	0.0975	0.39	0.012 - 6.25
<i>Citrobacter spp.</i>	4	**	**	0.024 - 0.0975
<i>Enterococcus faecalis</i>	11	**	**	0.3 - >25
<i>Streptococcus</i> β-hemolytic (Grp G)	22	0.39	1.56	0.006 - 3.12
<i>Streptococcus equisimilis</i>	10	**	**	0.003 - 0.78

*The correlation between the *in vitro* susceptibility data (MIC Values) and clinical response has not been determined.

**There were an insufficient number of isolates to calculate the MIC₅₀ or MIC₉₀.

Table 6: MIC Values* (µg/mL) of Orbifloxacin Against Dermal Pathogens Isolated Between 1994 and 1996 From Clinical Infections of Cats

Bacteria Name	Number of Isolates	MIC ₅₀	MIC ₉₀	MIC Range
<i>Staphylococcus intermedius</i>	25	0.39	0.39	0.024 - 3.125
<i>Staphylococcus aureus</i>	7	**	**	0.195 - 0.39
Coagulase +ve staphylococci	32	0.39	0.39	0.024 - 3.125
<i>Pasteurella multocida</i>	47	0.012	0.048	0.003 - 0.195
<i>Pseudomonas aeruginosa</i>	3	**	**	0.39 - 3.125
<i>Pseudomonas spp.</i>	10	**	**	0.195 - 6.25
<i>Escherichia coli</i>	17	0.048	0.195	0.024 - 25
<i>Enterobacter spp.</i>	12	**	**	0.024 - 0.78
<i>Enterococcus faecalis</i>	10	**	**	1.56 - 3.125
<i>Streptococcus</i> β-hemolytic (Grp G)	14	**	**	0.006 - 1.56

*The correlation between the *in vitro* susceptibility data (MIC Values) and clinical response has not been determined.

**There were an insufficient number of isolates to calculate the MIC₅₀ or MIC₉₀.

DRUG INTERACTIONS: Compounds (eg, sucralate, antacids, and multivitamins) containing divalent and trivalent cations (eg, iron, aluminum, calcium, magnesium, and zinc) may substantially interfere with the absorption of quinolones resulting in a decrease in product bioavailability. Therefore, the concomitant oral administration of quinolones with foods, supplements, or other preparations containing these compounds should be avoided.

CONTRAINDICATIONS: Orbifloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested, the dog being particularly sensitive to this side effect. Orbifloxacin is contraindicated in immature dogs during the rapid growth phase (between 2 and 8 months of age in small and medium-sized breeds, and up to 18 months of age in large and giant breeds).

Orbifloxacin is contraindicated in dogs and cats known to be hypersensitive to quinolones.

PRECAUTIONS: The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats. Quinolones should be used with caution in animals with known or suspected central nervous system (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation

which may lead to convulsive seizures. Quinolones have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

The safety of orbifloxacin in animals that are used for breeding or that are pregnant and/or lactating has not been demonstrated.

WARNINGS: For use in animals only. Do not exceed 7.5 mg/kg body weight per day in cats. Keep out of the reach of children.

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. 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.

TARGET ANIMAL SAFETY: Orbifloxacin administered to young, clinically healthy, adult dogs and cats at doses of 7.5 mg/kg, 22.5 mg/kg, and 37.5 mg/kg for 30 consecutive days was well tolerated. At the exaggerated doses of 22.5 and 37.5 mg/kg/day, orbifloxacin caused mild gastrointestinal effects (soft feces) in both male and female cats. Emesis (males only), diarrhea (males only), reduced food consumption with subsequent reduced body weight were evident in cats administered ORBAX® Tablets at 75 mg/kg/day for 10 days. Orbifloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested, the dog being particularly sensitive to this side effect. In 8- to 10-week-old beagle puppies dosed daily with orbifloxacin for 30 days, microscopic lesions consistent with fluoroquinolone-induced arthropathy of the articular cartilage was seen in only one of eight dogs dosed at 12.5 mg/kg, and in all eight dogs dosed at 25 mg/kg. (See **CONTRAINDICATIONS**.) No arthropathy was noted in 12-week-old kittens administered orbifloxacin at doses as high as 25 mg/kg for 1 month.

ADVERSE REACTIONS: In clinical trials, when the drug was administered at 2.5 mg/kg/day, no drug-related adverse reactions were reported.

Post Approval Experience: The following adverse reactions, although rare, are based upon voluntary post-approval reporting:

Hypersensitivity: facial edema, anaphylaxis/anaphylactoid reactions

Neurologic: seizures, ataxia

Behavioral: depression, lethargy

Gastrointestinal: vomiting, anorexia

HOW SUPPLIED: ORBAX® (orbifloxacin) Tablets are available in the following presentations:

5.7 mg: Bottles of 250 yellow tablets NDC 0061-1171-01

22.7 mg: Bottles of 250 green, E-Z Break, single-scored tablets NDC 0061-1141-01

68 mg: Bottles of 100 blue, E-Z Break, single-scored tablets NDC 0061-1174-01

STORAGE CONDITIONS: Store between 2° and 30°C (36° and 86°F). Protect from excessive moisture.

To report suspected adverse reactions, contact Schering-Plough Animal Health at 1-800-224-5318.

October 2005

B-19335658

Made in Canada.

Schering-Plough Animal Health Corp.,
Union, NJ 07083

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