June 18, 1997

FREEDOM OF INFORMATION SUMMARY

Supplemental New Animal Drug Applications

NADA 140-441

BAYTRIL® Antibacterial Tablets

enrofloxacin at 5.7, 22.7, and 68.0 mg per tablet

and

NADA 140-913

BAYTRIL® Antibacterial Injectable Solution

enrofloxacin 22.7 mg per mL

Sponsored by:

BAYER Corporation, Agriculture Division, Animal Health

I. GENERAL INFORMATION

NADA Numbers: 140-441 and 140-913

Sponsor: BAYER Corporation
Agriculture Division
Animal Health
P.O. Box 390
Shawnee, Kansas 66201

Established name: enrofloxacin tablets and enrofloxacin injectable solution

Trade name: BAYTRIL® Antibacterial Tablets and BAYTRIL® Antibacterial Injectable Solution

Marketing status: prescription

Effect of the Supplement:

The supplement to NADA 140-441, for dogs and cats, provides for revisions to 21 CFR 520.812 as indicated below.

Conditions of use - (1) *Amount.* Administer orally at a rate to provide 5 to 20 mg/kg (2.27 to 9.07 mg/lb) of body weight, either as a single daily dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals.

(2) *Indications* - Enrofloxacin tablets in dogs and cats for the management of diseases associated with bacteria susceptible to enrofloxacin. [This statement will replace section (2)(i) and (ii) as previously approved].

(3) *Limitations* - Treatment should be continued for at least 2 to 3 days beyond cessation of clinical signs, to a maximum of 30 days for both dogs and cats.

The supplement to NADA 140-913, for dogs, provides for revisions to 21 CFR 522.812 as indicated below.

(2) *Indications* - Enrofloxacin injectable solution in dogs for the management of diseases associated with bacteria susceptible to enrofloxacin.

II. INDICATIONS FOR USE

Baytril® Antibacterial Tablets and Injectable Solution are indicated for the management of diseases in dogs and cats associated with bacteria susceptible to enrofloxacin.

III. PRODUCT INFORMATION

A. Dosage form: 5.7 mg, 22.7 mg, and 68 mg enrofloxacin per tablet, and 22.7 mg per mL

B. Route of administration: Baytril Antibacterial Tablets for oral administration and Baytril Injectable Solution for intramuscular administration

C. Recommended dosage: The dose range of Baytril Antibacterial Tablets in dogs and cats is 5 to 20 mg/kg (2.27 to 9.07 mg/lb) of body weight, either as a single dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. The dose of Baytril Injectable Solution for dogs is 2.5 mg/kg (1.13 mg/lb) as a single injection. The injectable dose should be followed by oral tablet treatment in 12 hours.

IV. EFFECTIVENESS

A. Clinical efficacy of the recommended minimum dosages have been established in dogs as indicated and referenced in the Freedom of Information Summaries for NADA 140-441 dated January 24, 1989, May 4, 1990, and October 29, 1990, and NADA 140-913 dated January 29, 1990.

B. The drugs distribute widely and reach adequate blood and tissue concentrations in the target animal species. Tissue concentration values are found in the approved labels, and are presented, or referenced, in the Freedom of Information Summaries associated with these approvals.

The wide distribution and activity of these drugs would indicate that the drugs may be used in several conditions, and is evidenced by the wide range of recommended conditions, indications, and limitations in clinical literature as indicated in Table 1.

Table 1. The following literature supports the condition of use.

Usage	11 mg/kg BID for 4 days; n = 6 adult dogs
Article/ Journal Reference	Walker RD, Stein GE, Hauptman JG, et al. Pharmacokinetic evaluation of enrofloxacin administered orally to healthy dogs. Am J Vet Res 1992; 53:2315-2319.
Conclusions/ Explanation	-dosage of 11 mg/kg was required to maintain serum concentrations greater than the MIC_{90} of *Pseudomonas aeruginosa* for the entire dosing interval - no adverse reactions observed
Usage	100 dogs, 25 cats received 10 mg/kg/day, variable durations
Article/ Journal Reference	vom Hove W, Lettow E, Opitz M. Experiences with the anti-infective enrofloxacin (Baytril®) in pyodermas in dogs and cats. Kleintierpraxis 1992; 37:817-822.
Conclusions/ Explanation	- authors recommend 10 mg/kg/day for bacterial dermatoses, for at least 3 weeks, to be adapted to individual cases - dose was well-tolerated and can be safely administered over a period of several weeks

Usage	5 mg/kg BID, dogs and cats
Article/ Journal Reference	Aucoin D. Rational antimicrobial therapy in dermatitis. Proceedings of the 10th ESVD (European Soc. of Vet Derm) annual congress, Aalborg Denmark, 1993:116-125.
Conclusions/ Explanation	- recommends increasing to this dose from 5 mg/kg SID if no response is seen in 1 week - also notes that once or twice daily dosing is possible, depending on the MIC of the pathogen

Usage	5 - 7.5 mg/kg BID, dogs and cats
Article/ Journal Reference	Rosychuk R. Management of Otitis Externa. VetClinNorthAmSmallAnimPract; 1994;24:921-951(1994).
Conclusions/ Explanation	- this dose recommended for "enhanced effect [against Pseudomonas infections]" - "pending culture and sensitivity data, the systemic antibiotic of choice"

Usage	2.5 - 5 mg/kg BID, dogs
Article/ Journal Reference	Mason I. Selection and use of antibacterial agents in canine pyoderma. Practice 1993; 15:29-34.
Conclusions/ Explanation	- "in general, doses of antimicrobial agents are doubled for skin infections..."

Usage	5 mg/kg BID, dogs
Article/ Journal Reference	Dorfman M, Barsanti J, Budsberg S. Enrofloxacin concentrations in dogs with normal prostate and dogs with chronic bacterial prostatitis. Am J Vet Res 1995; 56:386-389.
Conclusions/ Explanation	- resulted in prostatic fluid and tissue concentrations exceeding the MIC of most pathogens that cause bacterial prostatitis

Usage	2.5 - 5.0 mg/kg q12-24h, dogs and cats
Article/ Journal Reference	McKellar Q. Clinical relevance of the pharmacologic properties of fluoroquinolones. Supplement to Compendium on Continuing Education for the Practicing Veterinarian 1996, 18(2):14-21.
Conclusions/ Explanation	- use a 5.0 mg/kg dose.

Usage	10 mg/kg BID, dogs and cats
Article/ Journal Reference	Ihrke P. Experiences with enrofloxacin in small animal dermatology. Supplement to Compendium on Continuing Education for the Practicing Veterinarian 1996, 18(2):35-39.
Conclusions/ Explanation	- given "occasionally," author notes "dosages have been effective and without adverse effects..." Also notes a study where enrofloxacin was administered BID for periods from 2 to 14 weeks, with excellent response in 93.3% of dogs (n=30). Author concludes: "extended regimen therapy with enrofloxacin has been used effectively for the management of recurrent deep pyoderma."

Usage	10 mg/kg SID or 5 mg/kg BID, dogs and cats
Article/ Journal Reference	Carlotti D. (Table of recent studies in:) New trends in systemic antibiotic therapy of bacterial skin disease in dogs. Supplement to Compendium on Continuing Education for the Practicing Veterinarian 1996, 18(2):40-47.
Conclusions/ Explanation	- given for duration of "3 weeks or more;" includes other doses given for durations of "1 - 12 weeks and 2 - 6 weeks."

Usage	2.5 - 5 mg/kg, q12h
Article/ Journal Reference	Hawkins E. Antibiotics for lower respiratory tract infections. Supplement to Compendium on Continuing Education for the Practicing Veterinarian 1996, 18(2):59-65.
Conclusions/ Explanation	- notes "increased dosage may be necessary for relatively resistant organisms;" she notes that "relatively high dosages of the drug (11 mg/kg q12h) have been recommended.

Usage	2.5 mg/kg BID, or 5 mg/kg SID
Article/ Journal Reference	Boothe D. Antimicrobial therapy in the critically ill patient. Supplement to Compendium on Continuing Education for the Practicing Veterinarian 1996, 18(2):66-83.

C. Support for a pharmacokinetic based dosage, and the addition of the dose range to the tablet formulation is presented below. Investigations into the pharmacodynamic properties of the fluoroquinolone class of antimicrobials indicate that bacterial killing is concentration-dependent (as opposed to time-dependent).

Results of the following studies indicated that the most reliable predictor of successful therapy with flouroquinolones is the concentration-dependent value described by the ratio of the peak concentration of the drug divided by the drug's mean inhibitory concentration for that pathogen (C_{max}/MIC).

1. Comparative study with enoxacin and netilmicin in a pharmacodynamic model to determine importance of ratio of antibiotic peak concentration to MIC for bactericidal activity and emergence of resistance. (Blaser J, Stone BB, Groner MC, et al. Antimicrob Agents Chemother 1987;31:1054-60.)

2. Pharmacokinetic consideration in quinolone therapy. (Nightingale CH. Pharmacotherapy 1993;13:34S-38S.)

3. Correlation of pharmacokinetic parameters to efficacy of antibiotics: Relationships between serum concentrations, MIC values, and bacterial eradication in patients with gram-negative pneumonia. (Schentag J. Scand J Infect Dis 74 (Suppl):218-234,1991.)

The following *in vivo* studies confirmed that total daily dose, and not frequency of administration, was significantly ($P < 0.05$) associated with bactericidal activity against *E. coli*, staphylococcal, and *P. aeruginosa* isolates.

4. Pharmacokinetics of enrofloxacin in clinically normal dogs and mice and drug pharmacodynamics in neutropenic mice with *Escherichia coli* and staphylococcal infections. (Meinen J, McClure J, Rosin E. Am J Vet Res 1995;56:1219-24.)

5. Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model of *Pseudomonas* sepsis. (Drusano G, Johnson D, Rosen M, et al. Antimicrob Agents Chemother 1993;37:483-90.)

Results of the following studies indicated that the area-under-the-inhibitory curve(AUIC), described by the quotient AUC/MIC, is useful for predicting the therapeutic efficacy of fluoroquinolone therapy. By simulation models and confirmatory clinical trials, the authors showed a 24-hour AUIC value ≥ 125 was the significant breakpoint for ensuring antibacterial activity capable of achieving both microbiological and clinical cures.

6. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. (Forrest A, Nix B, Ballow C, et al. Antimicrob Agents Chemother 1993;37:1073-81.)

7. Mathematical examination of dual individualization principles: the relationships between AUC above MIC and area under the inhibitory curve for cefmenoxime, ciprofloxacin and tobramycin. (Schentag J, Nix DE, Adelman MH. Pharmacother 1991;25:1050-1057.)

D. Conclusion: The published scientific literature, concerning fluoroquinolone antimicrobial agents, supports a greater spectrum of activity in bacteriocidal activity for enrofloxacin with the dose range and duration as provided by this supplement.

V. ANIMAL SAFETY

Safety of the dose range, for oral formulations, has been established in cats and dogs and is presented or referenced in the Freedom of Information Summaries for NADA 140-441. The information indicates that the tablets are safe within the dose range provided by this supplemental NADA. In several studies, the oral doses administered exceeded the recommended upper limit of the dose range for the tablet formulation. See Tables 2 and 3 which summarize the safety and toxicology studies filed in NADA 140-441.

Table 2. Baytril Tablets NADA 140-441 Safety trial summary for dogs.

Report #	Date	Study Title/Author	Total/no. per Group	Group	Dose	Duration	Conclusions
73146	May 85	Safety Evaluation of BAY Vp 2674; Subchronic (13 week) Feeding Study in the Dog - Porter	32/8	8 8 8	Avg = 52.0 Avg = 22.5 Avg = 9.1 mg/kg/day	91 to 94 d 91 to 94 d 91 to 94 d	Tolerated at all doses with no significant adverse effects. Sporadic emesis, inappetance.
73171	Aug 85	Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Puppies - Kohlenberg	12/4	4 4	20 10 mg/kg/day	14 d 14 d	No adverse effects at 20 mg/kg. Sporadic emesis, inappetance.
73219	Nov 85	Safety Evaluation for the Use of BAY Vp 2674 in *D. immitis* Microfilaria Positive Dogs - Kohlenberg	9/3	3 3	5 15 mg/kg/day	10 d 30 d	No effect on microfilaria or adult heartworms.
73229	Dec 85	Safety Evaluation for the Use of BAY Vp 2674 Tablets in Dogs - Kohlenberg	12/3	4 4 4	5 15 25 mg/kg/day	10 d 30 d 30 d	Safety margin of at least 5X [of the 2.5 mg/kg BID] dose for 3X [10 day] duration. Sporadic emesis, inappetance.
73355	June 86	Safety Evaluation for the Use of BAY Vp 2674 Tablets in Male Breeding Dogs - Stuke	9/3	3 3	5 15 mg/kg/day	10 d for 3 tx series /group	No adverse effect upon reproductive parameters.
73828	Dec 88	Safety Evaluation for BAY Vp 2674 in Female Breeding Dogs - Stuke and Magerkurth	15	5 6	5 15 mg/kg/day	10 d for 4 tx series /group	No adverse effects upon reproductive parameters
73775	Oct 87	Safety Evaluation of BAY Vp 2674; Repeat of a Subchronic (13 week) Feeding Study in the Dog [3 month old pups] - Porter	32/8	8 8 8	Avg = 75 Avg = 9.6 Avg = 3 mg/kg/day	91 d 91 d 91 d	- no death or moribundity; no effect on weight gain, food consumption, or clinical pathology parameters - joint lesions seen in high (2500) and mid-dose (320 ppm) pups - sporadic emesis, inappetance, loose stool
73788	June 88	Safety Evaluation of BAY Vp 2674: Subchronic (13 week) Feeding Study in Male Dogs [3 month old pups] - Porter	20/4	4 4 4 4	Avg = 0.3 Avg = 0.6 Avg = 1.2 Avg = 92 mg/kg/day	92 d 92 d 92 d 92 d	- no death or moribundity - decreased food consumption, inhibited weight gain in first weeks of study - overt toxicity limited to musculo-skeletal system

Table 3. Baytril Tablets NADA 140-441 Safety trial summary for cats.

Report #	Date	Study Title/Author	Total/no. per Group	Group	Dose	Duration	Conclusions
73768	June 88	Safety Evaluation for Concurrent Treatment of Cats with BAY Vp 2674 Oral Tablets and Other Commonly Used Feline Health Products - Kohlenberg	12/4	4 4 4	10 10 10 mg/kg/day	10 days 10 days 10 days	Compatible with commonly used feline health products
73793	Sept 88	General Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Cats - Kohlenberg	16	4 4 4	5 15 25 mg/kg/day	30 days 30 days 30 days	No adverse effects
73835	Nov 88	Safety Evaluation for the Use of BAY Vp 2674 Tablets in Young Kittens - Kohlenberg	12	4 4 4	5 15 25 mg/kg/day	30 days 30 days 30 days	No adverse effects
73597	May 86	General Safety in 8 - 10 week old Kittens - Hoffman and Karbe	15/5	5 5 5	5 15 25 mg/kg/day	15 days 15 days 15 days	No adverse effects

Conclusions: Enrofloxacin tablets have an adequate margin of safety in dogs and cats when administered over a dose range of 5 to 20 mg/kg for a maximum of 30 days.

VI. HUMAN SAFETY

A. Human Food Safety:

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of these NADAs. The drug is labeled for use in dogs and cats, which are non-food animals.

B. User Safety Concerns:

The labeling contains the following warning statement:

Human Warnings:
For use in animals only. Keep out of 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 exposures. 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. To report adverse reactions or to obtain a copy of the Material Safety Data Sheet, call 1-800-633-8405.

VI. AGENCY CONCLUSIONS

The data submitted in support of these NADAs 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 BAYTRIL® Antibacterial Tablets and BAYTRIL® Antibacterial Injectable Solution are safe and effective when used according to the approved conditions of use.

According to the Center's supplemental approval policy 21 CFR 514.106(b)(2)(iii), (iv), (v), & (ix), these are Category II changes that required a reevaluation of the safety and effectiveness data in the parent applications.

FDA has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. FDA's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (HFA-305).

VIII. APPROVED LABELING

A copy of the labeling is attached to this document.

A. Baytril (enrofloxacin) Antimicrobial Tablets No. 20, 500 tablet bottle, label

B. Baytril (enrofloxacin) Antimicrobial Tablets No. 20, 500 tablet bottle, package insert

C. Baytril (enrofloxacin) Antimicrobial Tablets No. 60, 250 tablet bottle, label

D. Baytril (enrofloxacin) Antimicrobial Tablets No. 60, 250 tablet bottle, package insert

E. Baytril (enrofloxacin) Injectable Solution, 20 mL vial, vial label, carton label, package insert