Date of Approval: February 23, 2001

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-441

BAYTRIL Antibacterial Tablets

BAYTRIL Taste Tabs Antibacterial Tablets

enrofloxacin

dogs and cats

The effect of this supplement is to (a) revise the dosage for cats on product labeling due to post-approval reports of retinal toxicity in cats, and, (b) provide for the addition of post-approval adverse drug experience information and fluoroquinolone class safety statements in labeling regarding retinal toxicity in cats.

Sponsored by:

Bayer HealthCare LLC

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I. GENERAL INFORMATION:

A. File Number:	NADA 140-441
B. Sponsor:	Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201 Drug Labeler Code: 000859
C. Proprietary Names:	BAYTRIL Antibacterial Tablets BAYTRIL Taste Tabs Antibacterial Tablets
D. Established Name:	Enrofloxacin
E. Pharmacological Category:	Antimicrobial
F. Dosage Forms:	Taste tablets and film-coated tablets
G. Amount of Active Ingredient:	Tablets are supplied as 22.7 mg, 68 mg and 136 mg enrofloxacin per tablet.
H. How Supplied:	Taste Tabs tablets - 22.7 mg, 68 mg,136 mg Film coated tablets - 22.7 mg, 68 mg
I. How Dispensed:	Rx
J. Dosages:	Cats: Administer orally at 5 mg/kg (2.27 mg/lb) of body weight. The dose for dogs and cats may be administered either as a single daily dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. Dogs: Administer orally at a rate to provide 5-20 mg/kg (2.27 to 9.07 mg/lb) of body weight. Selection of a dose within the range should be based on clinical experience, the severity of disease, and susceptibility of the pathogen. Animals which receive doses in the upper-end of the dose range should be carefully monitored for clinical signs that may include inappetance, depression, and vomition.
K. Route of Administration:	Oral

L. Species/Class:	Cats and dogs
M. Indication:	For the management of disease associated with bacteria susceptible to enrofloxacin.
N. Effect of Supplement:	This supplement lowers the dose in cats to 5 mg/kg (2.27 mg/lb) of body weight either as a single dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals, and provides for the addition of post-approval adverse drug experience information and fluoroquinolone class safety statements in labeling regarding retinal toxicity in cats.

II. EFFECTIVENESS:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 140-441 dated May 31, 1990 contains a summary of studies that demonstrate effectiveness of the drug for use in cats at a daily dose of 5 mg/kg body weight.

III. TARGET ANIMAL SAFETY:

The FOI Summary for the supplemental approval of NADA 140-441 dated May 31, 1990 contains a summary of studies that demonstrate safety of BAYTRIL tablets for use in cats at a daily dose of 5 mg/kg body weight.

The FOI Summary for the supplemental approval of NADA 140-441 dated June 18, 1997 allowed for the use of BAYTRIL tablets in cats at a dose range of 5-20 mg/kg daily.

Subsequent to approval of the 5-20 mg/kg dose range, post-approval drug experience report monitoring indicated that the use of BAYRTIL tablets in cats was associated with blindness. To further investigate this association Bayer conducted an ocular safety study in cats in 2000.

A. Ocular Safety Study in Cats

1. Study Title: Evaluation of the effects of oral BAYTRIL at three different dose levels on the vision of adult cats. Study 151.033

2. Type of Study: Five week feline ocular safety study; cats were dosed for 21 consecutive days

3. Study Facility: Bayer Animal Health
   DeSoto Animal Research Farm
   DeSoto, KS 66018

4. General Design:

   a. Purpose: The objective of this study was to evaluate the safety of orally administered BAYTRIL (enrofloxacin) on the vision of cats. BAYTRIL was administered orally at 5 mg/kg, 20 mg/kg, and 50 mg/kg of body weight per day for 21 consecutive days.

   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 6 to 8 months of age at the time of initiation of dosing.

c. *Placebo Control*: tap water

d. *Dosage Form:* BAYTRIL 22.7 mg and 68 mg taste tablets

e. *Dosage Used*:

Table 1. Dosing Groups

Test Groups	Cats/Sex	Dose (mg/kg/day)
Group A	2M, 2F	5 mg/kg, 1X
Group B	2M, 2F	20 mg/kg, 4X
Group C	3M, 1F	50 mg/kg, 10X
Group D	1M, 3F	0 mg/kg, control
Group E	2M, 2F	5 mg/kg, 1X
Group F	2M, 2F	20 mg/kg, 4X
Group G	2M, 2F	50 mg/kg, 10X
Group H	2M, 2F	0 mg/kg, control

f. *Route of Administration*: Oral

g. *Study Duration*: Cats in Groups A-D remained in the study for 3 weeks and cats in Groups E-H remained in the study for 5 weeks.

h. *Pertinent Measurements/Observation*: During the study ophthalmic exams were performed on Days 0, 4, 11, 18, 25, and 32. The following observations were also performed during the study: clinical observations, physical examination, body weight, electroretinographic (ERG) exams, electrocardiographic analysis, hematology, blood chemistry, FeLV/FIV testing, thyroxine (T4) levels, ocular histopathology, enrofloxacin plasma and vitreous humor concentrations, and taurine analysis.

5. Results:

Vomiting, salivation and depression were noted in the 20 and 50 mg/kg/day groups. Cats receiving 5 mg/kg/day of enrofloxacin had normal ophthalmic exams and no abnormalities noted on the electroretinograms (ERGs) throughout the study. There were no retinal histopathology changes detected in this group.

20 mg/kg groups
In the 20 mg/kg/day groups, 2 of 8 cats had abnormal findings on ERGs. In one of these two cats, the left eye was deemed unhealthy beginning Day 7 of treatment. ERG results showed decreased amplitude readings and prolonged latency times supportive of a retinopathy involving large areas of the retina. These ERG findings returned to acceptable amplitude and latency values (but not baseline levels) by Day 21. The other cat had abnormal

readings in both eyes after eight days of enrofloxacin administration. ERG tests were considered normal on Days 14 and 21.

Two other cats in this group had serious fundic lesions consisting of central retinal degeneration in one cat and generalized retinal degeneration in the other cat. An additional cat had histopathological retinal changes detected by light microscopy.

50 mg/kg groups
In the 50 mg/kg/day groups, 5 out of 8 cats had serious fundic lesions consisting of generalized retinal degeneration. Severe changes in amplitude were seen in 6 of 8 cats, and abnormal ERG findings were noted in all 8 cats at some time during the study. All 8 cats had histopathological retinal changes detected by light microscopy that were not reversible.

ERG readings in 3 cats on Days 7, 14, 21, 28, and 35 for both eyes were evaluated as severely unhealthy/blind (although one of these cats was terminated on Day 24) indicating blindness due to complete retinal degeneration. A fourth cat in this group had ERG tests evaluated as severely unhealthy/blind on all study days, except for the right eye on Day 21 which was in the normal range. Two cats in this group had ERG test results for the left and right eyes evaluated as severely unhealthy/blind on Days 7 and 14. The results for both eyes were evaluated as healthy on Day 21. One cat in this group had ERG results on Days 7, 14, 21, 28, and 35 evaluated for the left and right eye as partially unhealthy/blind. The eighth cat had ERG results on Days 7 and 14 evaluated as unhealthy; however ERG results on Days 21, 28, and 35 were evaluated as healthy.

6. Study Conclusions:

Retinal changes were not noted in cats administered a dose of 5 mg/kg/day of enrofloxacin for 21 days. Doses of 20 and 50 mg/kg/day of enrofloxacin in cats resulted in ocular abnormalities. The severity of findings were greatest in the 50 mg/kg groups.

It was concluded that a dose of 5 mg/kg/day should not be exceeded in cats as higher doses may cause retinal toxicity. This revised FOI Summary amends the June 18, 1997 FOI Summary wherein a dose range of 5-20 mg/kg/day was approved for use in dogs and cats. Although the 5-20 mg/kg/day dose range remains for dogs; the dose in cats has been lowered to 5 mg/kg (2.27 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.

B. Label Changes:

This supplemental approval lowers the dose in cats to the originally approved dose of 5 mg/kg (2.27 mg/lb) of body weight either as a single dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. Based on post-approval experience, in rare instances, use of this product in cats has

been associated with retinal toxicity. Cats should be carefully monitored for clinical signs of mydriasis and/or changes in the retina.

This FOI Summary indicates the return to the originally approved dose for use in cats and replaces the supplemental approval in 1997 allowing for use of a dose range (5-20 mg/kg daily dose).

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

> Post-Approval Experience: The following adverse experiences, although rare, are based on voluntary post-approval adverse drug experience reporting. The categories of reactions are listed in decreasing order of frequency by body systems.
> Ocular: Mydriasis, retinal degeneration (retinal atrophy, attenuated retinal vessels, and hyperreflective tapeta have been reported), loss of vision. Mydriasis may be an indication of impending or existing retinal changes.
> Gastrointestinal: vomiting, anorexia, elevated liver enzymes, diarrhea
> Neurologic: ataxia, seizures
> Behavioral: depression, lethargy, vocalization, aggression
>
> WARNINGS:
> For use in animals only. In rare instances, use of this product in cats has been associated with Retinal Toxicity. Do not exceed 5 mg/kg of body weight per day in cats. Safety in breeding or pregnant cats has not been established.
>
> PRECAUTIONS: The use of fluoroquinolones in cats has been reported to adversely affect the retina. Such products should be used with caution in cats.
>
> ANIMAL SAFETY SUMMARY:
> CATS:
> Enrofloxacin was administered to thirty-two (8 per group), six- to eight-month-old cats at doses of 0, 5, 20, and 50 mg/kg of body weight once a day for 21 consecutive days. There were no adverse effects observed in cats that received 5 mg/kg body weight of enrofloxacin. The administration of enrofloxacin at 20 mg/kg body weight or greater caused salivation, vomition, and depression. Additionally, dosing at 20 mg/kg body weight or greater resulted in mild to severe fundic lesions on ophthalmologic examination (change in color of the fundus, central or generalized retinal degeneration), abnormal electroretinograms (including blindness), and diffuse light microscopic changes in the retina.

IV. HUMAN FOOD 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, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to BAYTRIL tablets:

> 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 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.

VI. 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 BAYTRIL tablets, when used according to the label, are safe and effective for the management of diseases associated with bacteria susceptible to enrofloxacin. BAYTRIL Antibacterial Tablets are indicated for use in dogs and cats.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose and manage diseases associated with bacteria susceptible to enrofloxacin.

B. Exclusivity:

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

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

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