Date of Approval: July 24, 2012

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-068

BAYTRIL 100

Enrofloxacin
Injectable Solution
Beef and Non-Lactating Dairy Cattle

For the control of bovine respiratory disease (BRD) in beef and non-lactating dairy cattle at high risk of developing bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*

Sponsored by:

Bayer HealthCare LLC
Animal Health Division

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## I. GENERAL INFORMATION:

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|---|---|
| A. File Number: | NADA 141-068 |
| B. Sponsor: | Bayer HealthCare LLC<br>Animal Health Division<br>P.O. Box 390<br>Shawnee Mission, KS 66201<br><br>Drug Labeler Code: 000859 |
| C. Proprietary Name: | BAYTRIL 100 |
| D. Established Name: | Enrofloxacin |
| E. Pharmacological Category: | Antimicrobial |
| F. Dosage Form: | Injectable Solution |
| G. Amount of Active Ingredient: | 100 mg/mL |
| H. How Supplied: | 100, 250, and 500 mL bottles |
| I. How Dispensed: | Rx |
| J. Dosages: | Single-Dose Therapy (BRD Treatment): Administer once, a subcutaneous dose of 7.5 - 12.5 mg/kg of body weight (3.4 - 5.7 mL/100 lb).<br><br>Multiple-Day Therapy (BRD Treatment): Administer daily, a subcutaneous dose of 2.5 - 5.0 mg/kg of body weight (1.1 - 2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.<br><br>Single-Dose Therapy (BRD Control): Administer once, a subcutaneous dose of 7.5 mg/kg of body weight (3.4 mL/100 lb). |
| K. Route of Administration: | Subcutaneous injection |
| L. Species/Class: | Beef and non-lactating dairy cattle |

M. Indications:

Cattle - Single-Dose Therapy: BAYTRIL 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, *H. somni* and *M. bovis*.

Cattle - Multiple-Day Therapy: BAYTRIL 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* in beef and non-lactating dairy cattle.

N. Effect of Supplement:

This supplement provides for a new indication for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, *H. somni* and *M. bovis*.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

This supplemental approval does not change the previously approved 7.5 mg/kg BW single-dose dosage regimen for cattle. The Freedom of Information (FOI) Summary for the original approval of NADA 141-068 dated July 24, 1998, contains dosage characterization information for cattle.

### B. Substantial Evidence:

Dose Confirmation Study:

1. Title: "A Clinical Efficacy Study of BAYTRIL 100 Injectable Solution for the Control of Naturally Occurring Bovine Respiratory Disease Associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni,* and *Mycoplasma bovis* in Cattle with a High Risk of Developing the Disease". Study number 152.280. February 2010 to July 2010.

2. Investigators:
   Kelly F. Lechtenberg, DVM, PhD; Midwest Veterinary Services, Inc., Oakland, NE
   David Bechtol, DVM; Agri Research Center, Inc., Canyon, TX
   Breck Hunsaker, DVM, PhD; Summit Research, Wellington, CO
   Calvin Booker, DVM, MVetSc; Feedlot Health Management Services, Okotoks, Alberta, Canada
   Teresa Schieber, DVM; Midwest Veterinary Services, Inc., Oakland, NE
   Terry TerHune, DVM, PhD; HMS Veterinary Development, Inc., Tulare, CA

3. Study Design:

a) *Objective:* The objective of this study was to evaluate the effectiveness of BAYTRIL 100 injectable solution for the control of respiratory disease associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* in beef and non-lactating dairy cattle with a high risk of developing BRD.

b) *Study Animals:* A total of 1,150 commercial, crossbred, weaned beef-type calves (female and castrated male) were enrolled in the study. Calves were at least four months of age and weighed 137 to 350.9 kg at enrollment. Calves were in good health with no complicating injuries and no clinical signs of BRD at enrollment. Calves were subjected to the normal environmental conditions, feeding, and management practices of the location.

c) *Experimental Design:* The study was a randomized block design, with animals randomized to treatment and control groups based on order of appearance through the chute. Calves were assigned randomly to treatment groups and pens in groups of 10 (five BAYTRIL 100-treated and five saline-treated animals per pen). The individual animal was the experimental unit. The Investigator and personnel making clinical observations were masked to the treatment assignment.

d) *Test Article Administration:* The test article was BAYTRIL 100 (enrofloxacin) injectable solution, 100 mg enrofloxacin/mL, as the currently marketed U.S. formulation. The negative control article was sterile saline (0.9% NaCl) injectable solution.

Calves received a single subcutaneous dose in the neck of either BAYTRIL 100 at 7.5 mg/kg BW (n = 575 calves) or an equivalent volume of saline (0.075 mL/kg BW; n = 575 calves), administered at enrollment (Day 0). The maximum injection volume was 20 mL per injection site.

e) *Measurements and Observations:* On Day 0, calves were scored for signs of BRD and had rectal temperatures taken. Calves were enrolled if they had a depression score = 0 (on a scale of 0 [normal] to 3 [severe depression], and a respiratory score ≤ 1 (on a scale from 0 [normal] to 3 [severe respiratory distress], and a rectal temperature < 104.0 °F. In addition, the source group of calves experienced one or more risk factors, including:

- transportation with calves from multiple farm origins
- an extended transport time with few to no rest stops
- an temperature change of ≥ 30 °F from origin to study site
- a ≥ 30 °F fluctuation in environmental temperature at a study site within a 24-hour period
- exposure to wet or cold weather conditions.

Calves qualifying for enrollment were weighed and had a nasopharyngeal swab collected for microbial culture and isolation. Calves were observed daily on Days 1 through 14 and evaluated for treatment failure. Calves meeting the treatment failure criteria (a depression score = 1 or 2 or a

respiratory score = 2, and a rectal temperature ≥ 104.0 °F; or a depression or respiratory score = 3 regardless of rectal temperature) had a nasopharyngeal swab collected for microbial culture and isolation, and then were removed from the study. Lung tissue was collected from one calf that was euthanized during the study. Calves that remained in the study and were not removed as a treatment failure were classified as treatment successes on Day 14.

4. Statistical Analysis: The primary variable was Day 14 treatment success. Treatment success was evaluated using the GLIMMIX procedure in SAS. A binomial distribution of the primary outcome variable was assumed and a logit link was used. A two-sided test and an alpha of 0.05 were used as the level of significance.

   Mortality, isolation rate of specific pathogens, and prevalence and severity of BRD clinical signs (depression, respiratory score) were evaluated as secondary variables. Secondary variables were summarized as appropriate.

   For the addition of *M. bovis* to the BRD control indication, the effectiveness criteria were: 1) overall effectiveness for BRD, 2) at least 30 *M. bovis* isolates cultured from at least 30 different study animals, and 3) more treatment successes than failures in the group of animals positive for *M. bovis* on Day 0 that were treated with BAYTRIL 100.

5. Results: A total of 6 enrolled calves were excluded from the effectiveness analysis for protocol deviations or non-BRD related reasons. Treatment success was statistically significantly higher ($p = 0.0013$) in the BAYTRIL 100-treated group (497/573, 87.83%) than in the saline-treated control group (455/571, 80.92%).

   A total of 406, 406, 24, and 39 isolates of *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*, respectively, were recovered from nasopharyngeal swab samples and a single lung sample from enrolled calves. Presumptively identified *M. bovis* isolates were identified to the species level using a polymerase chain reaction (PCR) method.

   Numerically more treatment successes than treatment failures were observed in BAYTRIL 100-treated calves that cultured positive for *M. bovis* pretreatment. In the BAYTRIL 100-treated group, 16 calves cultured positive for *M. bovis* pre-treatment. Thirteen of the 16 calves (81%) were treatment successes and three calves (19%) were treatment failures.

   *H. somni* was determined to be acceptable for inclusion in the BRD control indication because 1) BAYTRIL 100 was previously demonstrated to be effective for the treatment of BRD associated with *H. somni*; 2) BAYTRIL 100 demonstrated effectiveness for the control of respiratory disease in beef and non-lactating dairy cattle with a high risk of developing BRD, in groups of calves in which *H. somni* was present; and 3) a well-reasoned scientific justification based upon the prevalence of *H. somni* among North American feedlot cattle enrolled in BRD field studies conducted between 2004 and 2010 showed analogous probabilities of isolating 24 or 30 isolates (the minimum number of *H. somni* isolates needed per the study protocol) of *H. somni*.

6. Adverse Events: No test-article related adverse events were reported.

7. Conclusion: This study demonstrates that BAYTRIL 100 administered as a single subcutaneous dose of 7.5 mg/kg BW is effective for the control of respiratory disease associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* in beef and non-lactating dairy cattle with a high risk of developing BRD.

## III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains a summary of target animal safety studies for cattle.

## IV. HUMAN FOOD SAFETY:

### A. Microbial Food Safety (Antimicrobial Resistance):

This supplemental approval allows for the addition of control for bovine respiratory disease (BRD) in cattle at high risk to the currently approved BAYTRIL 100 single-dose label. BAYTRIL 100 Injectable Solution (single dose of 7.5 mg/kg body weight) is currently approved for the treatment of BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Haemophilus somni*, and *Mycoplasma bovis* in beef and non-lactating dairy cattle. The current withdrawal period for the use of BAYTRIL 100 injectable in beef and nonlactating dairy cattle is 28 days.

The firm provided a qualitative microbial food safety risk assessment that included: 1) a *release assessment* to describe the probability that enrofloxacin and its use in the cattle production environment will result in emergence or selection of fluoroquinolone-resistant *Campylobacter* and *Salmonella spp.* attributed to the proposed use of enrofloxacin to treat cattle at high risk for BRD, and included specifically a thorough address of the spectrum of antibacterial activity of enrofloxacin, mechanisms of fluoroquinolone resistance in *Campylobacter* and *Salmonella*, the current prevalence of *Campylobacter* and *Salmonella* in cattle and retail beef; 2) an *exposure assessment* to describe the likelihood of human foodborne exposure to *Campylobacter and Salmonella* following consumption of ground beef from treated beef and non-lactating cattle, and 3) a *consequence assessment* to describe potential human health consequences arising from exposure to the defined foodborne pathogens or resistance determinants by considering the human medical importance of fluoroquinolones in the treatment of human gastrointestinal diseases.

Based upon the Agency's evaluation of the information submitted by the firm, and in consideration of the current fluoroquinolone and quinolone susceptibility profiles of *Salmonella spp.*, *E.coli,* and *Campylobacter spp.*, including their prevalence in the food commodity of concern (ground beef) and target animal (cattle), and taking into account the following factors that describe the targeted population at high risk for BRD:

- transportation of cattle from multiple farm origins
- an extended transport time with few to no rest stops

- an temperature change of ≥ 30 °F from origin to study site
- a ≥ 30 °F fluctuation in environmental temperature at a study site
- within a 24-hour period
- exposure to wet or cold weather conditions.

The Agency concludes that the use of enrofloxacin in cattle at high risk for BRD will not result in a significant risk to the development of fluoroquinolone resistance in foodborne *Campylobacter* and *Salmonella* originating from treated cattle.

Decision Statement:

The overall risk estimation associated with the use of enrofloxacin injectable in cattle under the proposed conditions of use is high, based on individual rankings of medium for the release assessment, medium for the exposure assessment, and high for the consequence assessment. The latter ranking of high for the consequence assessment is based on fluoroquinolones being critically important in human medicine as is the empiric drug class of choice to treat a majority of clinical gastrointestinal infections. However, the Agency thinks that the proposed use of enrofloxacin in cattle at high risk for BRD is adequately addressed by risk management strategies such as prescription only marketing status under the direction of a veterinarian, injectable route of administration, limited number of animals treated (individually), and monitoring by the National Antimicrobial Resistance System. The Agency therefore concludes that the proposed conditions of use and appropriate risk factors outlined above to determine if cattle are at high risk for BRD are adequate to support the use of enrofloxacin in beef and non-lactating cattle, and help ensure that risks to public health from fluoroquinolone-resistant *Campylobacter* and *Salmonella* originating from treated cattle are minimal.

B. Impact of Residues on Human Intestinal Flora:

The impact of enrofloxacin residues on human intestinal flora was previously assessed and a microbiological acceptable daily intake (mADI) was determined under a supplemental approval under NADA 141-068 dated February 13, 2008. It is briefly summarized below.

1. Determination of the need for establishing a microbiological ADI

a. Step 1: It was previously determined that enrofloxacin residues are active against representative human intestinal flora.

b. Step 2: It was previously determined that enrofloxacin residues enter the human colon.

c. Step 3: It was previously determined that enrofloxacin residues entering the human colon remain microbiologically active.

d. Step 4: It was previously determined that there was justification to eliminate testing for the endpoint of increases in the populations of resistant bacteria in the human colon.

2. Determination of the final Microbiological ADI

a. Determination of the fraction of oral dose available for microorganisms

Based on a fecal binding study data, there is a 2% fraction of the oral dose available to microorganisms.

b. Determination of the Microbiological ADI using NOAEC/L or $MIC_{calc}$

An mADI was determined using minimum inhibitory concentration (MIC) data to determine an effect by enrofloxacin residues. An $MIC_{calc}$ for enrofloxacin was determined at 0.189 mcg/ml. Therefore, given a fraction of oral dose available to microorganisms of 2%,

$$\text{ADI } (\mu\text{g/kg BW/day}) = \frac{MIC_{calc} \text{ X Mass of colon content}}{\text{Fraction of dose available X 60 kg}}$$

$$= \frac{0.189 \text{ X } 220}{0.02 \text{ X } 60}$$

= 34.65 mcg/kg BW/day or 2.08 mg/person/day

Decision Statement or Determination of Microbiological ADI:

The microbiological ADI is 34.65 mcg/kg BW/day or 2.08 mg/person/day.

C. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains summaries of all toxicology studies.

D. Assignment of the Final ADI:

Acceptable Daily Intake (ADI) of 0.003 mg/kg BW/day is based on a toxicological end point.

E. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

No reassessment of the safe concentrations for total residues was needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains information used to determine safe concentrations for total residues.

F. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-068 dated July 24, 1998, contains summaries of all residue chemistry studies for cattle.

G. Analytical Method for Residues:

The FOI Summary for the original approval of BAYTRIL 100 Injectable Solution (NADA 141-068), dated July 24, 1998, contains the analytical method summaries for enrofloxacin in cattle tissues.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to BAYTRIL 100:

> 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 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. For customer service or to obtain product information, including a Material Safety Data Sheet, call 1-800-633-3796. For medical emergencies or to report adverse reactions, call 1-800-422-9874.

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 100, when used according to the label, is safe and effective for control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis.* Additionally, data demonstrate that residues in food products derived from cattle treated with BAYTRIL 100 will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to control BRD, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date

of the approval. The three years of marketing exclusivity apply only to the new indication (control of BRD), for which this supplement is approved.

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.