Date of Approval: November 21, 2012

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-068

BAYTRIL 100 Injectable Solution

Enrofloxacin
Swine

For the treatment and control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*.

Sponsored by:

Bayer HealthCare LLC
Animal Health Division

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-068
B. Sponsor:	Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201 Drug Labeler Code: 000859
C. Proprietary Name:	BAYTRIL 100 Injectable Solution
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. Dosage:	Administer once, behind the ear, a subcutaneous dose of 7.5 mg/kg of body weight (3.4 mL/100 lb). Administered dose volume should not exceed 5 mL per injection site.
K. Route of Administration:	Subcutaneous injection
L. Species/Class:	Swine
M. Indications:	BAYTRIL 100 is indicated for the treatment and control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Mycoplasma hyopneumoniae*.
N. Effect of Supplement:	This supplement provides for the addition of two pathogens, *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae* to the SRD treatment and control indications.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the supplemental approval of NADA 141-068 dated March 14, 2008, contains dosage characterization information for swine.

B. Substantial Evidence:

1. *M. hyopneumoniae* Challenge Model Effectiveness Study

a. Title: "Efficacy and In Use Safety of BAYTRIL 100 for the Treatment of *Mycoplasma hyopneumoniae* Infection in Swine Using an Experimentally Induced Infection." Study 152.279, December 2009 to January 2010.

b. Investigator: Kelly F. Lechtenberg, DVM, PhD, Midwest Veterinary Services, Inc., Oakland, NE

c. Study Design:

1) *Objective:* The objective of this study was to demonstrate that a single subcutaneous (SC) dose of BAYTRIL 100 administered at 7.5 mg/kg BW has a specific therapeutic effect against *M. hyopneumoniae*.

2) *Study Animals:* A total of 140 commercial feeder pigs were sourced for the study, from which 132 pigs were challenged. Pigs were crossbred females and castrated males, 9 to 10 weeks of age, weighing 25.6 to 42 kg. Pigs received no medications or vaccines after arrival, and were acclimated at the study site for 4 days prior to challenge. Pigs were confirmed to be serologically negative for *M. hyopneumoniae* after arrival. Pigs were subjected to the normal environmental conditions, feeding methods, and management practices of the location.

3) *Experimental Design:* The study was a single location, placebo-controlled, masked, randomized challenge model study. The pig was the experimental unit. All pigs were challenged with an *M. hyopneumoniae* mucosal homogenate and were randomly assigned to one of twelve pens and one of three treatment groups (BAYTRIL 100 [36 pigs]; saline [36 pigs]; or a non-treated sentinel group [60 pigs]). The sentinel group pigs were also randomly assigned to necropsy order. The three treatment groups were commingled in each pen. Personnel making clinical observations and performing necropsies (the Investigator and any personnel collecting or recording data) were masked to treatment assignment.

4) *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.

Test and control articles were administered as an SC injection given behind the ear as a single dosage of 7.5 mg/kg BW (or equivalent volume of saline) on Day 0.

5) *Measurements and Observations:* General health observations were conducted twice daily from arrival through the end of the study. Following the acclimation period, all pigs were challenged on three consecutive days by endotracheal and intranasal administration of an *M. hyopneumoniae* mucosal homogenate. The homogenate contained a pathogenic strain of *M. hyopneumoniae* recovered in 2009 from a pig with typical *M. hyopneumoniae* lung lesions. Beginning 5 days after the initial challenge, pigs were evaluated daily for coughing. On the day that at least 5% of all pigs had a cough score (on a scale from 0 [absent] to 2 [repeated and marked coughing]) of 1 or greater for three consecutive days (Days -2, -1 and 0), five randomly-selected sentinel pigs were euthanized and necropsied to establish Day 0. Day 0 was defined as the day that at least 4 of 5 necropsied pigs each had a total lung lesion score of ≥ 5%.

   Pigs were clinically scored for cough, respiration (on a scale from 0 [normal] to 3 [severe respiratory distress]), and depression (on a scale of 0 [normal] to 3 [severe depression]) on Day 0 and then daily from Day 3 through Day 10. On Day 10, all study animals were euthanized, necropsied, and evaluated for lung lesions. The percentage of gross pneumonic lung lesions were determined for each lobe, and a total lung lesion score was calculated as a weighted score as follows: left apical lobe (10%), left cardiac lobe (10%), left diaphragmatic lobe (25%), right apical lobe (10%), right cardiac lobe (10%), right diaphragmatic lobe (25%), and accessory lobe (10%).

d. Statistical Analysis: The primary variable was the mean total lung lesion score. The lung lesion scores (transformed using the arcsine square root transformation) were analyzed using a linear mixed model with treatment as a fixed effect and pen as the random effect, using an alpha of 0.05 (two-sided).

e. Results: A statistically significant decrease ($p < 0.0001$) in the mean total lung lesion score was observed in the BAYTRIL 100 group (4%) compared to the saline group (27%).

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

g. Conclusion: This study demonstrates that BAYTRIL 100 administered as a single subcutaneous dose of 7.5 mg/kg BW had a specific effect (i.e., decrease in mean total lung lesion score in the enrofloxacin-treated group compared to the saline-treated group) against *M. hyopneumoniae*.

2. SRD Treatment Field Study

a. Title: "A Clinical Efficacy Study of BAYTRIL 100 Injectable Solution for the Treatment of Naturally-Occurring Swine Respiratory Disease Associated

with *Mycoplasma hyopneumoniae*." Study 152.314, September 2010 to November 2010.

b. Investigators:

Site 1: Kelly F. Lechtenberg, DVM, PhD; Midwest Veterinary Services, Inc., Oakland, NE
Site 2: Terry TerHune, DVM, PhD; HMS Veterinary Development, Inc., Tulare, CA

c. Study Design:

1) *Objective:* The objective of this study was to demonstrate the effectiveness of a single SC dose of BAYTRIL 100 administered at 7.5 mg/kg BW for the treatment of naturally-occurring SRD associated with *M. hyopneumoniae*.

2) *Study Animals:* A total of 299 (Site 1) and 300 (Site 2) crossbred female and castrated male feeder pigs were sourced from Nebraska (Site 1) and South Dakota (Site 2), from which 75 pigs were enrolled in each treatment group at each site. Pigs were acclimated at the study site for 3 days (Site 1) or 56 days (Site 2) prior to enrollment. On Day 0, pigs at Site 1 were approximately 8 weeks old and weighed 12 to 25.5 kg, and pigs at Site 2 were approximately 15 weeks old and weighed 15.5 to 66 kg. Pigs were subjected to the normal environmental conditions, feeding methods, and management practices of the location.

3) *Experimental Design:* The study was a two-site, placebo-controlled, masked, randomized field study. The pig was the experimental unit. At each site, pigs meeting enrollment criteria were randomly assigned to one of 15 pens and one of two treatment groups (BAYTRIL 100 [75 pigs]) or saline [75 pigs]) on Day 0. Treatment groups were commingled in each pen (5 pigs from each group in each pen). Personnel making clinical observations and performing necropsies (the Investigator and any personnel collecting or recording data) were masked to treatment assignment.

4) *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.

Test and control articles were administered as an SC injection given behind the ear as a single dosage of 7.5 mg/kg BW (or equivalent volume of saline) on Day 0. The maximum injection volume was 5 mL per injection site.

5) *Measurements and Observations:* Pigs with a depression score of ≥ 2 (on a scale of 0 [normal] to 3 [severe depression]) and a respiratory score ≥ 2 (on a scale from 0 [normal] to 3 [severe respiratory distress]) and a rectal temperature ≥ 104.0 °F were weighed,

randomized to treatment groups, and treated (Day 0). General health observations were conducted once daily on the day of arrival and Day 7, and twice daily on the day following arrival through Day 6. Pigs were observed for adverse events once daily on Days 0 and 7, and twice daily on Days 1 through 6. Pigs that had signs of worsening SRD (i.e., severe respiratory distress or severe depression), injury, or signs of non-SRD conditions necessitating humane removal were removed, euthanized, and necropsied. Pigs completing the study on Day 7 were weighed, assigned a depression score and a respiratory score, and had a rectal temperature recorded. Then they were euthanized, necropsied, and had lung tissue collected for the presence of *M. hyopneumoniae* and other SRD pathogens.

Confirmation that *M. hyopneumoniae* was present in the source herd was obtained by PCR and/or culture of lung tissue from representative animals prior to Day 0. PCR was used to confirm the presence or absence of *M. hyopneumoniae* in nasal swabs collected at enrollment and lung tissue collected at necropsy. Samples were also collected from the lung at necropsy for isolation of other bacterial SRD pathogens.

d. Statistical Analysis: The primary variable was the Day 7 treatment success rate. Treatment success was defined as an animal that was not removed from the study for SRD from Days 1 to 7, and that had a depression score ≤ 1 and a respiratory score ≤ 1 and a rectal temperature < 104 °F on Day 7. The effect of treatment on the percent success was evaluated using the GLIMMIX procedure in SAS (SAS Institute, Cary, NC). The model used treatment as a fixed effect and pen nested in site as a random effect. The two sites were analyzed independently.

e. Results: At Site 1, there were more successes (46/75, 61.3%) in the enrofloxacin-treated group than in the control group (20/75, 26.7%). At Site 2, there were more successes (69/75, 92%) in the enrofloxacin-treated group than in the control group (25/75, 33.3%). The difference was statistically significant at each site ($p < 0.0001$).

A total of 26 *M. hyopneumoniae* isolates were identified. A total of 83 *B. bronchiseptica* isolates were also identified. Currently labeled pathogens, including *Actinobacillus pleuropneumoniae* (6 isolates), *Haemophilus parasuis* (43 isolates), *Pasteurella multocida* (4 isolates), and *Streptococcus suis* (12 isolates) were also isolated from pigs in this study.

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

g. Conclusion: This study demonstrates that BAYTRIL 100 administered as a single SC dose of 7.5 mg/kg BW is effective for the treatment of SRD associated with *B. bronchiseptica* and *M. hyopneumoniae*.

3. SRD Control Field Study

a. Title: "A Clinical Efficacy Study of BAYTRIL 100 Injectable Solution for the Control of Naturally-Occurring Swine Respiratory Disease Associated with *Mycoplasma hyopneumoniae*." Study 152.315, October 2010.

b. Investigator: Kelly F. Lechtenberg, DVM, PhD; Midwest Veterinary Services, Inc., Oakland, NE

c. Study Design:

1) *Objective:* The objective of this study was to demonstrate the effectiveness of a single SC dose of BAYTRIL 100 administered at 7.5 mg/kg BW for the control of naturally-occurring SRD associated with *M. hyopneumoniae*.

2) *Study Animals:* A total of 447 crossbred female and castrated male feeder pigs were sourced from Nebraska, from which 400 pigs were enrolled in the study. On Day 0, pigs were approximately 6 weeks old and weighed 16 to 43.5 kg. Pigs were subjected to the normal environmental conditions, feeding methods, and management practices of the location.

3) *Experimental Design:* The study was a single-site, placebo-controlled, masked, randomized field study. The pen was the experimental unit. When at least 15% of the candidate herd had a depression score of ≥ 2 (on a scale of 0 [normal] to 3 [severe depression]) and a respiratory score ≥ 2 (on a scale from 0 [normal] to 3 [severe respiratory distress]) and a rectal temperature ≥ 104.0 °F, pigs were assigned to pens (sick pigs first, followed by the remaining pigs) such that 5 or 6 pigs per pen had clinical signs of SRD and 14 or 15 pigs per pen were not sick. Pens were randomly assigned to one of two treatment groups (BAYTRIL 100 [200 pigs]) or saline [200 pigs]). Each pen contained 20 pigs, and within a pen, all pigs received the same treatment. Personnel making clinical observations and performing necropsies (the Investigator and any personnel collecting or recording data) were masked to treatment assignment.

4) *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.

Test and control articles were administered as an SC injection given behind the ear as a single dosage of 7.5 mg/kg BW (or equivalent volume of saline) on Day 0. The maximum injection volume was 5 mL per injection site.

5) *Measurements and Observations:* Pigs were weighed, randomized to treatment groups, and treated on Day 0. Pigs were observed for general health and adverse events once daily on Days 0 and 7, and twice daily on Days 1 through 6. Pigs that had signs of worsening SRD

(i.e., severe respiratory distress or severe depression), injury, or signs of non-SRD conditions necessitating humane removal were removed, euthanized, and necropsied. Pigs completing the study on Day 7 were weighed, assigned a depression score and a respiratory score, and had a rectal temperature recorded. Then they were euthanized, necropsied, and had lung tissue collected for the presence of *M. hyopneumoniae* and other SRD pathogens.

Confirmation that *M. hyopneumoniae* was present in the source herd was obtained by PCR and/or culture of lung tissue from representative animals prior to Day 0. PCR was used to confirm the presence or absence of *M. hyopneumoniae* in nasal swabs collected at enrollment and lung tissue collected at necropsy. Samples were also collected from the lung at necropsy for isolation of *M. hyopneumoniae*, *A. pleuropneumoniae*, *B. bronchiseptica*, *H. parasuis*, *P. multocida*, and *S. suis*.

d. Statistical Analysis: The primary variable was the Day 7 treatment success rate. Treatment success was defined as an animal that was not removed from the study for SRD from Days 1 to 7, and that had a depression score ≤ 1 and a respiratory score ≤ 1 and a rectal temperature < 104 °F on Day 7. The effect of treatment on the percent success per pen, transformed using the arcsine square root transformation, was evaluated using a general linear mixed model in SAS (SAS Institute, Cary, NC). The statistical model included treatment as a fixed effect.

e. Results: Two saline-treated pigs were removed from the study. One pig was removed and euthanized on Day 2 for a rectal prolapse. One pig was found dead on Day 6 and was diagnosed with intestinal torsion. Both pigs were removed from the analysis.

The treatment success rate was statistically significantly higher ($p < 0.0002$) in the BAYTRIL-treated group (70.0%) than in the saline-treated group (48.5%).

A total of 4 *M. hyopneumoniae* isolates were identified. A total of 242 *B. bronchiseptica* isolates were also identified. *M. hyopneumoniae* and *B. bronchiseptica* isolate numbers were combined across the treatment and control field studies (Studies 152.314 and 152.315) for consideration as labeled pathogens. Currently labeled pathogens, including *H. parasuis* (67 isolates), *P. multocida* (14 isolates), and *S. suis* (9 isolates) were also isolated from control study (Study 152.315) pigs.

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

g. Conclusion: This study demonstrates that BAYTRIL 100 administered as a single SC dose of 7.5 mg/kg BW is effective for the control of SRD associated with *B. bronchiseptica* and *M. hyopneumoniae*.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-068 dated March 14, 2008, contains a summary of target animal safety studies for swine.

IV. HUMAN FOOD SAFETY:

A. Microbial Food Safety (Antimicrobial Resistance):

CVM did not require additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-068 dated March 14, 2008, contains a summary of all information used to assess the risk to microbial food safety (antimicrobial resistance).

B. Impact of Residues on Human Intestinal Flora:

CVM did not require additional information for the impact of residues on human intestinal flora for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-068 dated February 13, 2008, contains a summary of all information used to assess the impact of residues on human intestinal flora.

C. Toxicology:

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-068 dated February 13, 2008, contains a summary of all toxicology studies and information.

D. Assignment of the Final Acceptable Daily Intake (ADI):

The final ADI is the toxicological ADI of 0.003 mg/kg BW/day or 0.2 mg/person/day for total enrofloxacin residues derived from the NOEL of 3 mg/kg BW/day from a subchronic oral toxicity study in dogs (Study No. 73775), and a safety factor of 1000.

E. Safe Concentrations for Total Residues (edible tissues):

The safe concentration of total enrofloxacin residues in each edible tissue of swine is 0.6 ppm for muscle, 1.8 ppm for liver, 3.6 ppm for kidney, and 3.6 ppm for fat.

F. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 141-068 dated March 14, 2008, contains a summary of residue chemistry studies for swine.

G. Analytical Method for Residues:

The FOI Summary for the supplemental approval of NADA 141-068 dated March 14, 2008, contains the analytical method summaries for enrofloxacin in swine.

V. USER SAFETY:

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

> Not for use in humans. 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. 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 Injectable Solution, when used according to the label, is safe and effective for the treatment and control of SRD associated with *B. bronchiseptica* and *M. hyopneumoniae.* Additionally, data demonstrate that residues in food products derived from swine treated with BAYTRIL 100 Injectable Solution 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 treat and control SRD, 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 applies only to the indications for treatment and control of SRD associated with *Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*, 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.