Date of Approval: August 18, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-244

DRAXXIN Injectable Solution

(tulathromycin)

To add *Mycoplasma bovis* to the list of target pathogens for the bovine respiratory disease (BRD) treatment indication.

Sponsored by:
Pfizer, Inc.

I. GENERAL INFORMATION:

A. File Number:	NADA 141-244
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name:	DRAXXIN Injectable Solution
D. Established Name:	Tulathromycin
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Sterile injectable solution
G. Amount of Active Ingredient:	100 mg/mL
H. How Supplied:	100 mL, 250 mL, and 500 mL glass vials
I. How Dispensed:	Rx
J. Dosage:	2.5 mg/kg body weight (BW), administered once
K. Route of Administration:	Subcutaneous (cattle) injection in the neck
L. Species/Class:	Beef and non-lactating dairy cattle
M. Indications:	DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*), and *Mycoplasma bovis;* and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*).
N. Effect of Supplement:	To add *Mycoplasma bovis* to the list of target pathogens for the bovine respiratory disease (BRD) treatment indication.

II. EFFECTIVENESS:

A. Dosage Characterization:

The Center for Veterinary Medicine (CVM) did not require dosage characterization for this supplemental approval. The FOI Summary for the original approval of DRAXXIN Injectable Solution (NADA 141-244) dated May 24, 2005, contains dosage characterization information for cattle.

B. Substantial Evidence:

Effectiveness of tulathromycin for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*); and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*) was previously demonstrated in the original approval, and is summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244) dated May 24, 2005.

Effectiveness of tulathromycin for the treatment of BRD associated with *M. bovis* was demonstrated using two experimentally-induced infection model studies and examining *M. bovis* data from cattle used in the studies for the original approval of DRAXXIN Injectable Solution.

1. "Evaluation of Tulathromycin to Treat BRD Associated with *M. bovis* in Calves". Study 5131E-03-03-264. October 2003.

a. Type of Study: Induced infection model effectiveness study. The study was conducted in accordance with the VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary and Medicinal Products (VICH GL9) "Good Clinical Practice" Guideline.

b. Study Investigator and Location: Dr. A. Rae, Ph.D., Moredun Scientific Limited, Pentlands Science Park, Penicuik, Scotland.

c. Study Design:

1) Objective: To evaluate the effectiveness of DRAXXIN (tulathromycin) Injectable Solution administered subcutaneously (SC) once at a dose of 2.5 mg/kg body weight (BW) for the treatment of induced *M. bovis* respiratory infections in calves.

2) Test Animals: Seventy calves (male and female) of various dairy and dairy/beef cross breeds were enrolled. Calves were between 3 to 9 weeks of age on the first day of challenge, and weighed between 92.4 and 169.4 lbs on the day of treatment administration. All calves were negative for *M. bovis* by polymerase chain reaction (PCR) and serology prior to challenge.

3) *Experimental Design:* A 12 mL culture (1 x 10^8 cfu/mL) of *M. bovis* (Strain 16150 from Kansas State University [isolated in 1999], tulathromycin MIC 1 µg/mL) was administered intratracheally on three consecutive days.

   Calves that exhibited pyrexia (temperature ≥ 103.1 °F) and abnormal respiration (score of mild, moderate, or severe) within five days after the last inoculation were randomly assigned to treatment groups in a 1:1 ratio.

4) *Treatment Groups:*

Group	Treatment	Dosage	No. of Animals
T01	saline	0.025 mL/kg BW[1] SC once	35
T02	tulathromycin	2.5 mg/kg BW SC once	35

[1]volume equivalent to T02 dosage

5) *Test Article Administration:* The test article was tulathromycin (CP-472,295) sterile injectable solution. The control article was commercial physiological saline (0.9% sodium chloride) sterile injectable solution. Treatments were administered subcutaneously in the right side of the neck once on Day 0.

6) *Measurements and Observations:* The primary variable for effectiveness was the percentage of total lung with lesions typical of a *M. bovis* infection. Secondary variables were duration of post-treatment pyrexia, peak rectal temperature, body weight gains, mortality rates, isolation rate of *M. bovis*, prevalence and severity of clinical signs of respiratory disease, and presence of other respiratory pathogens from bronchial lavage samples.

   From the day before the first inoculation to the day of study completion (Day 14), calves were observed daily for clinical signs of respiratory disease including pyrexia, abnormal respiration, and depression. On Day 14, study calves were weighed and euthanized. At necropsy, gross examination of lungs was conducted. The percentage of total lung with lesions typical of a *M. bovis* infection was recorded, using the following percentages, which are based on the ratio of individual lung lobes to total lung mass: left apical 5%, left cardiac 6%, left diaphragmatic 32%, right apical 6%, right accessory 5%, right cardiac 7%, right diaphragmatic 35%, and intermediate 4% (reference: Jericho, K.W. and E.V. Langford. 1982. Aerosol Vaccination of Calves with *Pasteurella haemolytica* against Experimental Respiratory Disease. Can J. Comp. Med. 46 (3): 287-292). In addition, bronchial and lung lavage samples were collected for quantification (cfu/mL) of *M. bovis*, confirmation of the presence of

M. bovis antigen (using PCR), and isolation of other bacterial respiratory pathogens.

7) *Statistical Analysis:* For the percentage of total lung with lesions, peak rectal temperature, number of days with pyrexia, *M. bovis* isolation rate, and body weight gain, an analysis of variance was used to test the effect of treatment. The percentage of total lung with lesions was transformed (arcsine square root) prior to analysis. Rectal temperature was analyzed using an analysis of variance for repeated measures to test the effects of treatment, day, and treatment by day. For severity of clinical signs on Days 0, 2, and 14, a categorical model for repeated measures was used where the marginal probabilities were modeled to test the effects of treatment, day, and treatment by day. For the association between treatment and mortality, Fisher's exact test was used. Treatment differences were assessed at the 5% level of significance.

d. Results: Fifty-one of seventy calves (17 control, 34 tulathromycin) completed the study. The remaining 19 calves (18 control, 1 tulathromycin) were euthanized on welfare grounds.

1) *Lung Lesion Percentage:* Mean total lung lesion scores were significantly ($P = 0.0001$) lower in the tulathromycin-treated calves (11.3%) compared to the saline-treated calves (28.9%).

2) *Rectal Temperature:* Tulathromycin-treated calves had a significant ($P < 0.05$) reduction in rectal temperature compared to saline-treated calves from Day 1 to Day 7 inclusive.

3) *Body Weight Gains:* Body weight gains were higher in tulathromycin-treated calves (8.8 kg) compared to saline-treated calves (6.7 kg), but this difference was not significant ($P = 0.0786$).

4) *Mortality:* Mortality was significantly ($P < 0.0001$) lower in the tulathromycin-treated calves (1 of 35, 2.9%) than in the saline-treated calves (18 of 35, 51.4%).

5) *Isolation Rate of M. bovis:* The number of *M. bovis* recovered from lung lavage at necropsy was significantly ($P = 0.0084$) lower in the tulathromycin- treated calves ($10^{5.8}$ cfu/mL) than in the saline-treated calves ($10^{6.5}$ cfu/mL).

6) *Prevalence and Severity of BRD:* There were no differences in the distribution of abnormal respiration scores ($P = 0.2665$) or depression scores ($P = 0.5445$) between treatments.

7) *Other Respiratory Pathogens: Pasteurella multocida* was recovered from the lung lavage samples of 33 calves (22 control and 11 tulathromycin). No other bacteria were recovered from any other calf during the study.

e. Adverse Reactions: No test article related adverse reactions were reported. Other clinical abnormalities, including scours, lameness, swollen scrotum, hair loss, open sores, and ocular discharge were reported. These abnormalities were sporadic, occurred in both groups, and are not considered unusual for calves of this age.

f. Conclusion: DRAXXIN (tulathromycin) Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, was effective for the treatment of induced *M. bovis* respiratory disease.

2. Efficacy of Tulathromycin Injectable Solution for Treatment of Experimentally-Induced *Mycoplasma bovis* Infection in Cattle. Study 1131C-60-04-441. March 2005.

a. Type of Study: Induced infection model effectiveness study. The study was conducted in accordance with FDA Good Clinical Practice guidelines.

b. Study Investigator and Location: Kelly F. Lechtenberg, D.V.M., Ph.D., Midwest Veterinary Services, Inc. – North Farm, Lyons, NE

c. Study Design:

1) *Objective:* To investigate the effectiveness of tulathromycin injectable solution administered as a single subcutaneous (SC) dose of 2.5 mg/kg body weight (BW) for the treatment of BRD associated with experimentally-induced *M. bovis* infection in cattle.

2) *Test Animals:* Ninety-six male Holstein calves, 4 to 9.5 weeks old at enrollment, weighing 86.5 to 142.5 lbs, were used in the study. All calves were negative for *M. bovis* by PCR and serology prior to challenge.

3) *Experimental Design:* Candidate calves were inoculated with 30 mL of inoculum containing 1 x 10^8 CFU/mL ± 1 $\log_{10}$ *M. bovis* organisms endotracheally for three consecutive days, beginning on Day -3. The *M. bovis* isolate, MFS-5 (tulathromycin MIC of 0.5 µg/mL), was originally cultured in 2004 from a BRD mortality case at a Nebraska feedlot. Calves with a rectal temperature ≥ 103 °F and abnormal respiration (score of mild, moderate, or severe) were randomly assigned to treatment groups in a 1:1 ratio.

4) *Treatment Groups:*

Group	Treatment	Dosage	No. of Animals
T01	saline	0.025 mL/kg BW[1] SC once	48
T02	tulathromycin	2.5 mg/kg BW SC once	48

[1]volume equivalent to T02 dosage

5) *Test Article Administration:* The test article was tulathromycin (CP-472,295(e)) sterile injectable solution. The control article was commercial physiological saline (0.9% sodium chloride) sterile injectable solution. Treatments were administered subcutaneously in the left side of the neck once on Day 0.

6) *Measurements and Observations:* The primary variable for effectiveness was the percentage of total lung with lesions. Secondary variables were percent days with rectal temperature >103 °F, percent days with abnormal clinical scores, and body weight gain.

From Study Day 1 through Study Day 14, rectal temperature, attitude score, and respiratory scores were recorded for each animal. On Day 14, all animals were weighed, euthanized, and necropsied. The percentage of total lung with lesions typical of a *M. bovis* infection was recorded, using the following percentages, which are based on the ratio of individual lung lobes to total lung mass: left apical 5%, left cardiac 6%, left diaphragmatic 32%, right apical 6%, right accessory 5%, right cardiac 7%, right diaphragmatic 35%, and intermediate 4% (reference: Jericho, K.W. and E.V. Langford. 1982. Aerosol Vaccination of Calves with *Pasteurella haemolytica* against Experimental Respiratory Disease. Can J. Comp. Med. 46 (3): 287-292). Lung tissues and lavage samples were taken from each animal. Samples were cultured for *M. bovis*, *P. multocida*, *M. haemolytica*, and *H. somni*. MICs were determined for each pathogen.

7) *Statistical Analysis:* For the percentage of total lung lesions, percent days with pyrexia, and percent days with abnormal clinical scores, an analysis of variance was used to test the effect of treatment. All percentage data was transformed (arcsine square root) prior to analysis. For rectal temperature and body weight, an analysis of variance for repeated measures was used to test the effects of treatment, day, and treatment by day. Treatment differences were assessed at the 5% level of significance.

d. Results: No calves died or were euthanized during the study. One calf was removed due to a protocol deviation.

1) *Lung Lesion Percentage:* Mean total lung lesion scores were significantly ($P < 0.0001$) lower in the tulathromycin-treated calves (15.0%) compared to the saline-treated calves (30.7%).

2) *Rectal Temperature:* Tulathromycin-treated calves showed a significant ($P = 0.0003$) reduction in percentage of days with rectal temperatures > 103 ^{o}F (19.0% vs. 37.3%). Mean rectal temperature was significantly less ($P < 0.05$) in the tulathromycin-treated group compared to saline-treated calves on 12 of the 14 post-treatment days.

3) *Abnormal Clinical Scores:* Tulathromycin-treated calves had significantly fewer days with abnormal attitude scores (39.3% vs. 72.3%, $P <0.0001$) and significantly fewer days with abnormal respiratory scores (49.9% vs. 88.3%, $P <0.0001$) than did saline-treated calves.

4) *Body Weight Gains:* Tulathromycin-treated calves gained significantly more weight during the 14-day post-treatment period than did saline-treated calves (10.3 vs. 4.7 lb, $P = 0.0002$).

5) *Microbiological Results:* Cultures from lung tissue at necropsy (Day 14) identified *Mannheimia haemolytica* in 3 saline and 1 tulathromycin-treated calves, *Pasteurella multocida* in 9 saline and 4 tulathromycin-treated calves, and *Histophilus somni* in 2 saline-treated calves.

e. Adverse Reactions: No test article related adverse reactions were reported. Other clinical abnormalities, including stiffness (1 saline-treated calf) and lameness (7 saline/6 tulathromycin-treated calves) diagnosed as arthritis due to *M. bovis* were seen. Head tilts due to middle ear infections (4 saline/3 tulathromycin-treated calves) were also observed. These findings are common sequellae to *M. bovis* infection.

f. Conclusion: DRAXXIN (tulathromycin) Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, was effective for the treatment of induced *M. bovis* respiratory disease.

3. Comparison of Success Rates in Cattle with Natural BRD Infections

The success (cure) rate of calves with *M. bovis* isolated during the therapeutic studies (1133C-60-99-306, 1133C-60-99-307, and 1133C-60-99-308) summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244) dated May 24, 2005, was examined. None of the isolates obtained from the Texas site (1131C-60-99-305) survived the transport to the laboratory.

M. bovis was identified by fluorescent antibody (FA) assay in cultures from pre-treatment nasopharyngeal swabs. A total of 79 FA-positive isolates were found from calves in the tulathromycin and saline treatment groups. Of the

52 tulathromycin-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.

These findings demonstrate that DRAXXIN (tulathromycin) Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, is effective for the treatment of BRD in calves naturally infected with *M. bovis*.

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 141-244 dated May 24, 2005, contains a summary of target animal safety studies for cattle.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of all toxicology studies.

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of residue chemistry studies for cattle.

C. Microbial Food Safety:

The impact of the proposed change in the treatment indication for tulathromycin in cattle from "For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni (Haemophilus somnus)*" to "For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni (Haemophilus somnus)*, and *Mycoplasma bovis*" on microbial food safety was carefully considered by the Agency. The Agency determined that this change should not significantly impact public health, and therefore an evaluation of microbial food safety regarding this change was not necessary at this time.

D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains the analytical method summaries for tulathromycin in cattle.

V. USER SAFETY:

Human warnings are provided on the product labeling as follows:

For use in animals only. Not for human use. Keep out of reach of children.

To request a material safety data sheet, call 1-800-733-5500.

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 DRAXXIN Injectable Solution, when used according to the label, is safe and effective for the treatment of bovine respiratory disease (BRD) associated with *Mycoplasma bovis*. Additionally, data demonstrate that residues in food products derived from cattle treated with DRAXXIN Injectable Solution will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

Labeling restricts this drug to use by or on order of a licensed veterinarian. 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 BRD or 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 treatment of BRD associated with *Mycoplasma bovis* 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:

Tulathromycin is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
6,329,345	November 18, 2019
6,420,536	May 29, 2018
6,514,945	January 24, 2021

6,583,274	May 2, 2020
6,777,393	May 29, 2018

VII. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

a. DRAXXIN Injectable Solution – 100 mL vial label and insert
b. DRAXXIN Injectable Solution – 100 mL carton
c. DRAXXIN Injectable Solution – 250 mL vial label and insert
d. DRAXXIN Injectable Solution – 250 mL carton
e. DRAXXIN Injectable Solution – 500 mL vial label and insert
f. DRAXXIN Injectable Solution – 500 mL carton