Date of Approval: August 28, 2008

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-244

DRAXXIN Injectable Solution

Tulathromycin
Beef and non-lactating dairy cattle
and swine

For the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef and non-lactating dairy cattle.

Sponsored by:

Pfizer, Inc.

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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(s):	DRAXXIN Injectable Solution
D. Established Name(s):	Tulathromycin
E. Pharmacological Category:	Antimicrobial
F. Dosage Form(s):	Sterile injectable solution
G. Amount of Active Ingredient(s):	100 mg/mL
H. How Supplied:	50 mL, 100 mL, 250 mL, and 500 mL glass vials
I. How Dispensed:	Rx
J. Dosage(s):	2.5 mg/kg body weight (BW), administered once
K. Route(s) of Administration:	Subcutaneous (cattle) or intramuscular (swine) injection in the neck
L. Species/Class(es):	Beef and non-lactating dairy cattle, and swine

M. Indication(s):

Beef and Non-lactating Dairy Cattle:

BRD - DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis;* and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis*.

IBK - DRAXXIN Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.

Foot Rot - DRAXXIN Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef and non-lactating dairy cattle.

Swine:

DRAXXIN Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis,* and *Mycoplasma hyopneumoniae*.

N. Effect(s) of Supplement:

This supplement provides for a new indication, for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef and non-lactating dairy cattle.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-244 dated May 24, 2005, contains dosage characterization information for cattle.

B. Substantial Evidence:

1. Dose Confirmation Study

a. Title: "Clinical Efficacy of Tulathromycin Injectable Solution Against Naturally Occurring Bovine Interdigital Necrobacillosis." Study Number 1133C-60-06-573. April 2007 to June 2007.

b. Study Investigator and Location: Kelly F. Lechtenberg, D.V.M., Ph.D., Midwest Veterinary Service, Inc., Oakland, NE

c. Study Design:

1) *Objective:* To evaluate the effectiveness of a single subcutaneous (SC) administration of tulathromycin at a dose of 2.5 mg/kg body weight (BW), compared with saline-treated controls, for the treatment of bovine foot rot.

2) *Test Animals:* A total of 100 crossbred beef cattle (female and castrated male) were enrolled. Animals ranged from 10 to 14 months of age, and weighed 595 to 1195 lbs at enrollment. Study animals were obtained from two commercial feedlots in Nebraska. Enrolled animals had no history of foot rot in the 30 days prior to enrollment. Vaccination for *Fusobacterium necrophorum* was not permitted; otherwise, the typical vaccination program was followed. No antimicrobials or anti-inflammatory agents (including in-feed antimicrobials) were administered for at least 14 days prior to enrollment.

3) *Experimental Design:* Pens of cattle were evaluated daily as part of the normal feedlot practice. Cattle identified as lame were presented as potential study candidates to be scored by study personnel. Study candidates with a lameness score of 2 or 3 and a swelling score of 2 or 3 and a lesion score of 2 or 3 (using the scoring scales described below) in one foot only (the "qualifying foot") for two consecutive days were enrolled in the study. Cattle were assigned to treatment group according to a generalized block design and treated on the day they met the enrollment criteria (Day 0). Personnel conducting the foot rot evaluations were masked to the treatment assignments.

4) *Treatment Groups:*

Table 1. Summary of treatment groups.

Treatment	Dosage	No. of animals
saline (control)	0.025 mL/kg BW* SC as a single injection on Day 0	50
tulathromycin	2.5 mg/kg BW SC as a single injection on Day 0	50

*volume equivalent to tulathromycin administered at 2.5 mg/kg BW

5) *Test Article Administration:* The test article was DRAXXIN (tulathromycin) Injectable Solution, 100 mg/mL (commercial formulation). The control article was 0.9% sterile saline injectable solution. Test and control articles were administered by SC injection in the lateral neck once on Day 0.

6) *Measurements and Observations:* Clinical signs of foot rot (lameness, swelling, and lesions) were recorded for all four feet of each animal on Days -1 and 0. At enrollment, samples were collected from the affected interdigital lesions by swab and needle biopsy. General health observations were conducted from Day 1 to Day 7. Post-treatment lameness scores were recorded for all four feet of each animal on Days 2, 4, and 7. Post-treatment swelling and lesion scores were recorded for all four feet of each animal on Day 7.

   The following scoring scales were used:

   Lameness Scores: 0 = no lameness noted; 1 = favors foot, but moves readily; 2 = puts minimal weight on foot and moves slowly; 3 = holds foot up, reluctant to put weight on foot or move.

   Swelling Scores: 0 = none, no swelling observed; 1 = slight, swelling observed only in the interdigital space; 2 = moderate, swelling involving the interdigital space and swelling extending into the soft tissue below the dewclaws; 3 = severe, swelling observed in the interdigital space and around the dewclaws; coronary band on one or both toes is red and swollen; ascending swelling and cellulitis may extend above the dewclaws.

   Lesion Scores: 0 = no lesion; 1 = lesion healed or healing; 2 = small ($\leq$ ¼ the length of the interdigital space) necrotic lesion; 3 = medium (¼ to ¾ the length of the interdigital space) necrotic lesion; 4 = large ($\geq$ ¾ the length of the interdigital space) necrotic lesion.

d. Statistical Analysis: The primary variable was treatment success rate. The individual animal was the experimental unit. A treatment success was defined as an animal that had a reduction from Day 0 to Day 7 of two or more scores in lameness (i.e., 3 to 1, 3 to 0, or 2 to 0), and a swelling score of 0 or 1 on Day 7, and a lesion score of 0 or 1 on Day 7 in the qualifying foot. If an animal developed lameness, lesions, or swelling due to bovine foot rot in any non-qualifying foot during the study, that foot had to have scores of 0 for lameness, lesions, and swelling on Day 7 for the animal to be classified as a treatment success.

   Success was analyzed using a generalized linear mixed effect model with a binomial distribution and logit link. The model included the fixed effect of treatment and random effects of block and residual. The difference in success rate between treatments was evaluated at the 0.05 level of significance.

e. Results: All enrolled cattle were included in the analysis. The percentage of animals classified as a treatment success was significantly higher ($p < 0.0001$) in the tulathromycin-treated group (30/50, 60%) compared to the control group (4/50, 8%). A total of 55 *F. necrophorum* and 41 *Porphyromonas levii* isolates were identified from swab and biopsy samples.

f. Adverse Reactions: No test article-related adverse reactions were observed during the study.

g. Conclusion: The results of this study indicate that DRAXXIN Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, is effective for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *F. necrophorum* and *P. levii*.

2. Dose Confirmation Study

a. Title: "Clinical Efficacy of Tulathromycin Injectable Solution Against Naturally Occurring Bovine Interdigital Necrobacillosis." Study Number 1133C-02-06-568. May 2007 to July 2007.

b. Study Investigator and Location: Calvin W. Booker, D.V.M., M.Vet.Sc., Chinook Feeders Ltd., Okotoks, Alberta, Canada

c. Study Design:

1) *Objective:* To evaluate the effectiveness of a single SC administration of tulathromycin at a dose of 2.5 mg/kg BW, compared with saline-treated controls, for the treatment of bovine foot rot.

2) *Test Animals:* A total of 101 crossbred beef cattle (female and castrated male) were enrolled. Animals ranged from 8 to 18 months of age, and weighed 625 to 1185 lbs at enrollment. Study animals were owned by the feedlot. Enrolled animals had no history of foot rot in the 30 days prior to enrollment. Vaccination for *F. necrophorum* was not permitted; otherwise, the typical vaccination program was followed. No antimicrobials or anti-inflammatory agents (including in-feed antimicrobials) were administered for at least 14 days prior to enrollment.

3) *Experimental Design:* Pens of cattle were evaluated daily as part of the normal feedlot practice. Cattle identified as lame were presented as potential study candidates to be scored by study personnel. Study candidates with a lameness score of 2 or 3 and a swelling score of 2 or 3 and a lesion score of 2 or 3 (using the scoring scales described in Section II.B.1 above) in one foot only (the "qualifying foot") for two consecutive days were enrolled in the study. Cattle were assigned to treatment group according to a generalized block design and treated on the day they met the enrollment criteria (Day 0). Personnel conducting the foot rot evaluations were masked to the treatment assignments.

4) *Treatment Groups:*

Table 2. Summary of treatment groups.

Treatment	Dosage	No. of animals
saline (control)	0.025 mL/kg BW* SC as a single injection on Day 0	51
tulathromycin	2.5 mg/kg BW SC as a single injection on Day 0	50

*volume equivalent to tulathromycin administered at 2.5 mg/kg BW

5) *Test Article Administration:* The test article was DRAXXIN (tulathromycin) Injectable Solution, 100 mg/mL (commercial formulation). The control article was 0.9% sterile saline injectable solution. Test and control articles were administered by SC injection in the lateral neck once on Day 0.

6) *Measurements and Observations:* Clinical signs of foot rot (lameness, swelling, and lesions) were recorded for all four feet of each animal on Days -1 and 0. At enrollment, samples were collected from the affected interdigital lesions by swab and needle biopsy. General health observations were conducted from Day 1 to Day 7. Post-treatment lameness scores were recorded for all four feet of each animal on Days 2, 4, and 7. Post-treatment swelling and lesion scores were recorded for all four feet of each animal on Day 7.

d. Statistical Analysis: The primary variable was treatment success rate. The individual animal was the experimental unit. A treatment success was defined as an animal that had a reduction from Day 0 to Day 7 of two or more scores in lameness (i.e., 3 to 1, 3 to 0, or 2 to 0), and a swelling score of 0 or 1 on Day 7, and a lesion score of 0 or 1 on Day 7 in the qualifying foot. If an animal developed lameness, lesions, or swelling due to bovine foot rot in any non-qualifying foot during the study, that foot had to have scores of 0 for lameness, lesions, and swelling on Day 7 for the animal to be classified as a treatment success.

Success was analyzed using a generalized linear mixed effect model with a binomial distribution and logit link. The model included the fixed effect of treatment and random effects of block and residual. The difference in success rate between treatments was evaluated at the 0.05 level of significance.

e. Results: A total of 31 enrolled cattle were removed from the analysis due to protocol deviations, leaving 70 cattle included in the analysis. The percentage of animals classified as a treatment success was significantly higher ($p = 0.0088$) in the tulathromycin-treated group (30/36, 83.3%) compared to the control group (17/34, 50%). A total of 61 *F. necrophorum* and 62 *P. levii* isolates were identified from swab and biopsy samples.

f. Adverse Reactions: No test article-related adverse reactions were observed during the study.

g. Conclusion: The results of this study indicate that DRAXXIN Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, is effective for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *F. necrophorum* and *P. levii*.

3. Identification of Bacterial Isolates and Determination of Mean Inhibitory Concentrations (MICs)

a. Title: "Identification and Susceptibility Testing of Anaerobic Bacteria from Clinical Cases of Bovine Foot Rot from a Field Trial of DRAXXIN (tulathromycin)." Study Number 1671R-60-06-424. October 2007 to December 2007.

b. Methods: Foot rot pathogens were cultured from swabs and biopsy samples from animals enrolled in Study 1133C-60-06-573 and Study 1133C-02-06-568. Classical biochemical methods were used to definitively identify isolates of *F. necrophorum*. Classical biochemical methods were used to presumptively identify isolates as either *Prevotella* or *Porphyromonas* spp. with definitive identification based on the 16S ribosomal RNA gene sequence compared against the Ribosomal Database Project (RDP) database. Identification to the species level was confirmed if the gene sequence had ≥ 99% identity with gene sequences of previously defined species listed in the RDP database.

Tulathromycin minimum inhibitory concentrations (MICs) for *F. necrophorum* and *P. levii* were determined using the reference agar dilution method described by the Clinical and Laboratory Standards Institute (CLSI) document M11-A6.

c. Results: A total of 116 isolates were identified as *F. necrophorum* and 103 isolates were identified as *P. levii*. The MIC_{50}, MIC_{90}, and MIC range for each indicated pathogen species are shown in Table 3. Tulathromycin demonstrated *in vitro* activity against both of the bacterial species that were isolated from cattle with clinical signs of bovine foot rot enrolled in the pivotal effectiveness studies.

Table 3. Tulathromycin MIC values* of indicated pathogens isolated from cattle with naturally occurring bovine foot rot.

Indicated pathogens	Year of isolation	Number of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
F. necrophorum	2007	116	2	64	≤ 0.25 to >128
P. levii	2007	103	8	128	≤ 0.25 to 128

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

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 to approved tulathromycin (as DRAXXIN Injectable Solution) to include the new indication "for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef and non-lactating dairy cattle" was carefully considered by the Agency. The Agency determined that the addition of this new indication should not significantly impact public health, and therefore an evaluation of microbial food safety 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:

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

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 foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef and non-lactating dairy cattle. 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 the 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 bovine foot rot and (b) restricting this drug to use by or on the 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 bovine foot rot indication 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:

DRAXXIN Injectable Soultion 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 24, 2019
6,514,945	January 24, 2021
6,583,274	May 2, 2020
6,777,393	May 29, 2018

VII. ATTACHMENTS:

Facsimile Labeling:

a. DRAXXIN Injectable Solution – 50 mL vial label and insert
b. DRAXXIN Injectable Solution – 50 mL carton
c. DRAXXIN Injectable Solution – 50 mL shipper label
d. DRAXXIN Injectable Solution – 100 mL vial label and insert
e. DRAXXIN Injectable Solution – 100 mL carton
f. DRAXXIN Injectable Solution – 100 mL shipper label
g. DRAXXIN Injectable Solution – 250 mL vial label and insert
h. DRAXXIN Injectable Solution – 250 mL carton
i. DRAXXIN Injectable Solution – 250 mL shipper label
j. DRAXXIN Injectable Solution – 500 mL vial label and insert
k. DRAXXIN Injectable Solution – 500 mL carton
l. DRAXXIN Injectable Solution – 500 mL shipper label