Date of Approval: September 8, 2009

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-244

DRAXXIN Injectable Solution

Tulathromycin
Swine

For the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.

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:	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:	50 mL, 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:	Intramuscular injection in the neck
L. Species/Class:	Swine
M. Indications:	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*; and **for the control of SRD associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida,* and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.**

N. Effect of Supplement: This supplement provides for a new indication, "for the control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed."

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 swine.

B. Substantial Evidence:

The effectiveness of DRAXXIN (tulathromycin) injectable solution for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, and *Haemophilus parasuis* was demonstrated in the original approval of NADA 141-244 and is summarized in the FOI Summary dated May 24, 2005. The effectiveness of DRAXXIN for the treatment of SRD associated with *Mycoplasma hyopneumoniae* was demonstrated in a supplemental approval of NADA 141-244 and is summarized in the FOI Summary dated December 28, 2007.

A multi-site natural infection field study was conducted to confirm the effectiveness of DRAXXIN for the control of SRD in groups of pigs where SRD has been diagnosed.

1. Dose Confirmation Study

a. Title: "Evaluation of DRAXXIN Injectable Solution for the Control of Swine Respiratory Disease." Study Number 1123C-60-07-279. December 2007 to May 2008.

b. Investigators:

Lyle Kesl, DVM, PhD; Veterinary Resources, Inc., Ames, IA
Kelly Lechtenberg, DVM, PhD; Midwest Veterinary Services, Oakland, NE
Murray Pettitt, PhD; Prairie Swine Centre, Saskatoon, Saskatchewan, Canada
Ryan Saltzman, DVM; Veterinary Resources, Inc., Ames, IA
Teresa Schieber, DVM; Midwest Veterinary Services, Oakland, NE
Paul Yeske, DVM; Swine Veterinary Center, St. Peter, MN

c. Study Design:

1) *Objective:* To evaluate the effectiveness of DRAXXIN (tulathromycin) injectable solution for the control of SRD in groups of pigs where SRD has been diagnosed.

2) *Test Animals:* A total of 455 female and castrated male commercial crossbred feeder pigs less than 6 months old, weighing 20.6 to 98.7 lbs, were enrolled across six study sites. Each investigator purchased study candidates from commercial swine operations that had previously experienced an SRD outbreak and transported them to the study site.

3) *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. Treatments were administered by intramuscular (IM) injection in the lateral neck. The following table summarizes the treatment groups.

Table 2.1. Summary of treatment groups.

Group	Treatment Regimen	No. of Animals
T01	saline; 0.025 mL/kg body weight (BW)* IM as a single injection on Day 0	228
T02	tulathromycin; 2.5 mg/kg BW IM as a single injection on Day 0	227

*volume equivalent to tulathromycin at 2.5 mg/kg BW

4) *Measurements and Observations:* Study candidates were evaluated daily for clinical signs of SRD. An outbreak of SRD was defined as the day (Day 0) when at least 15% of study candidates in a pen had a respiratory score ≥ 2 (on a scale of 0 to 3 where 0 is normal), and a depression score ≥ 2 (on a scale of 0 to 3 where 0 is normal), and a rectal temperature of ≥ 104 °F. The first pig in a pen meeting the SRD criteria was euthanized and necropsied to characterize the disease outbreak; euthanized animals did not count towards the 15% needed to initiate treatment. When the pen met the 15% outbreak threshold, the remaining pigs in the pen were assigned to treatment groups and treated with tulathromycin or saline.

General health observations were conducted by a veterinarian or his/her designee once daily until enrollment was complete, twice daily from Day 0 through Day 6, and once on Day 7. All pigs remaining in the pen on Day 7 were clinically evaluated for respiratory score, depression score, and rectal temperature, and then were euthanized and necropsied. A pig was classified as a treatment success on Day 7 if it was alive and had a respiratory score ≤ 1, and a depression score ≤ 1, and a rectal temperature

of < 104 °F. Pigs that were not classified as treatment successes were classified as treatment failures.

At necropsy, the percentage of pneumonic lung lesions was estimated and a weighted lung lesion score was determined using the following ratios of individual lung lobes to total lung mass: left cranial 10%, left middle 10%, left caudal 25%, right cranial 10%, right middle 10%, right caudal 25%, and accessory 10%. Lung tissues and lung swabs were collected from each pig for bacterial culture and identification. Lung tissue was also evaluated by fluorescent antibody test for *M. hyopneumoniae*.

The individuals performing clinical assessments and necropsies were masked to treatment and did not participate in treatment administration.

d. Statistical Analysis: The individual animal was the experimental unit. Pigs were assigned to treatment based on a randomized complete block design. Treatment groups were commingled in pens.

The primary variable for evaluating effectiveness was treatment success rate. Lung lesion percentage and mortality were evaluated as secondary variables. Treatment success was analyzed using a generalized linear mixed model (GLIMMIX) in SAS. The model included the fixed effect of treatment and the random effects of site, site by treatment, block within pen, pen within site, and residual. Back-transformed least squares means were estimated and 95% confidence intervals were reported. A one-sided 5% level of significance ($p \leq 0.05$) was used to assess statistical significance.

e. Results:

A total of 453 enrolled pigs were included in the analysis. Two pigs were removed from the study for non-SRD reasons and were excluded from the effectiveness analysis.

1) *Treatment Success*: The percentage of pigs classified as a treatment success was statistically significantly higher ($p = 0.0488$) in the tulathromycin-treated group (132/226, 59.2%) compared to the control group (96/227, 41.2%).

2) *Lung Lesion Percentage*: The percentage of total lung with lesions was lower in the tulathromycin-treated group (6.6%) compared to the control group (13.1%).

3) *Mortality:* The number of mortalities associated with SRD was lower in the tulathromycin-treated group (4/226, 1.8%) compared to the control group (11/227, 4.8%).

4) *Microbiology:* At least 30 isolates of *A. pleuropneumoniae*, *P. multocida*, and *M. hyopneumoniae* were isolated from at least 30 pigs across the study sites. A total of 69/452 pigs (15.3% of lung samples) were positive by fluorescent antibody testing for *M. hyopneumoniae*.

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

g. Conclusion: Based on the results of this study, DRAXXIN (tulathromycin) injectable solution administered as a single IM dosage of 2.5 mg tulathromycin/kg BW was effective for the control of SRD associated with *A. pleuropneumoniae*, *P. multocida*, and *M. hyopneumoniae* in groups of pigs where SRD has been diagnosed.

2. Determination of Minimum Inhibitory Concentrations (MICs)

The MICs of tulathromycin were determined for the *A. pleuropneumoniae* and *P. multocida* isolates identified from lung swabs and lung tissue samples obtained from tulathromycin- and saline-treated pigs enrolled in the control of SRD field study (Study 1133C-60-07-279).

The methods used to determine the MICs were those described in the M31-A3 Clinical and Laboratory Standards Institute (CLSI) approved standard. The MIC_{50}, MIC_{90}, and MIC range for each indicated pathogen are shown in Table 2.2.

Table 2.2. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from SRD field studies in the U.S. and Canada.

Indicated pathogens	Year isolated	No. of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Actinobacillus pleuropneumoniae	2007 to 2008	88	16	16	4 to 32
Pasteurella multocida	2007 to 2008	40	1	2	≤ 0.03 to 2

* 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 swine.

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 swine.

C. Microbial Food Safety:

The Agency carefully reviewed information provided by the sponsor regarding microbial food safety associated with the use of tulathromycin as a single intramuscular injection at a dose of 2.5 mg/kg BW in swine for control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed. At this time, extremely low contamination rates of retail pork meat, combined with epidemiological evidence that the populations of *Campylobacter coli* found in pigs do not overlap appreciably with the populations found in human infections, indicate that the potential for human infection with erythromycin-resistant *Campylobacter* from consumption of pork is low, even though the prevalence of erythromycin-resistant *Campylobacter* in swine is quite high. Risk management considerations for this approval are all consistent with those of a Category 1 drug, with the exception of a medium extent of use; however, evidence presented by the sponsor regarding exposure and tulathromycin usage supports a medium extent of use for this Category 1 drug. The Agency concludes that there should not be an increased risk to human health due to antimicrobial resistance issues associated with the indication for tulathromycin use in swine.

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 swine.

The validated regulatory methods for detection and confirmation of residues of tulathromycin are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to DRAXXIN (tulathromycin) 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 control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed. Additionally, data demonstrate that residues in food products derived from swine 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 control swine respiratory disease 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 control of swine respiratory disease 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 Solution 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

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

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