Date of Approval: July 9, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-349

DRAXXIN 25 Injectable Solution

Tulathromycin

Swine

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

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-349

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

DRAXXIN 25 Injectable Solution

D. Established Name

Tulathromycin

E. Pharmacological Category

Antimicrobial

F. Dosage Form:

Injectable Solution

G. Amount of Active Ingredient

25 mg/mL

H. How Supplied

50 mL, 100 mL, and 250 mL bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

2.5 mg/kg body weight (BW), given as a single intramuscular (IM) injection

K. Route of Administration

Intramuscular (IM) injection

L. Species/Class

Swine

M. Indications

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.

II. EFFECTIVENESS

A. Dosage Characterization

The dosage regimen for DRAXXIN 25 Injectable Solution in swine is identical to the dosage regimen for DRAXXIN Injectable Solution (100 mg tulathromycin/mL, NADA 141-244). The Freedom of Information (FOI) Summary for the approval of DRAXXIN Injectable Solution dated May 24, 2005, contains dosage characterization information for swine. DRAXXIN 25 Injectable Solution contains 25 mg tulathromycin/mL.

B. Substantial Evidence

1. Pharmacokinetic Study

   a. Title: Pharmacokinetic Comparison of DRAXXIN Injectable Solution and a Lower Concentration Formulation of DRAXXIN Injectable Solution Administered to Swine by Intramuscular Injection at 2.5 mg Tulathromycin/kg Body Weight (study #1522N-60-11-382; January 2012 to June 2012).

   b. Study Director: Wendy Collard, Ph.D., Pfizer Animal Health, Kalamazoo, MI.

   c. Study Design:

      (1) *Objective*: To assess plasma bioequivalence of the currently-approved DRAXXIN Injectable Solution (NADA 141-244, 100 mg tulathromycin/mL) to DRAXXIN 25 Injectable Solution [lower concentration formulation (25 mg tulathromycin/mL)] in swine administered by intramuscular (IM) injection at 2.5 mg tulathromycin/kg BW.

      (2) *Animals*: 64 healthy pigs (32 barrows and 32 gilts) weighing 17 to 24.7 kg at the beginning of the study.

      (3) *Experimental Design*: This two-treatment parallel study compared pharmacokinetic (PK) characteristics of DRAXXIN 25 Injectable Solution (25 mg/mL) to the currently-approved DRAXXIN Injectable Solution (100 mg/mL). Blood samples were collected from each animal between 0 and 24 hours prior to dose administration, and at 20 and 40 minutes, and 1, 1.5, 2, 3, 4, 7, 10, 24, 48, 96, 144, 192, 240, 288, and 336 hours after dosing.

      (4) *Test Article Administration*: Animals were dosed intramuscularly in the neck at 2.5 mg/kg BW once with one of the two treatments.

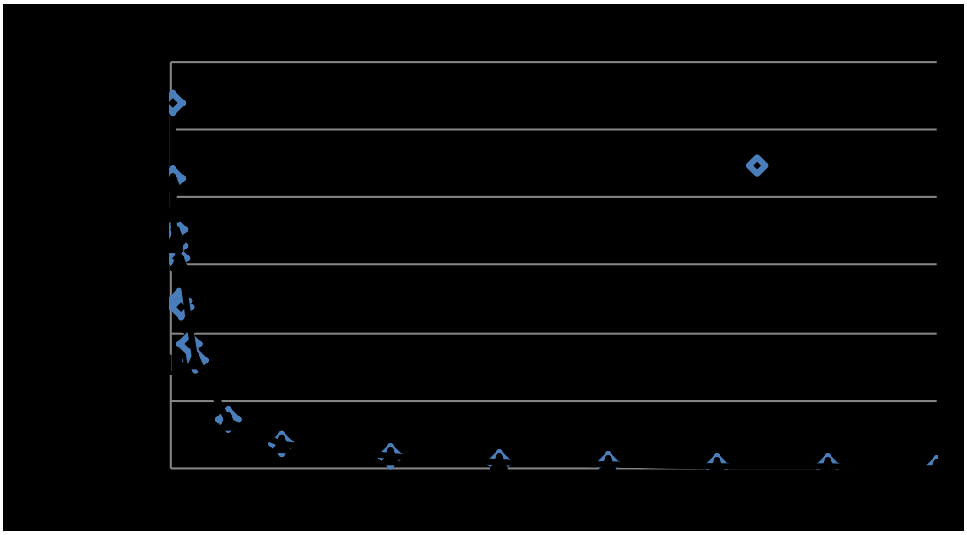
(5) *Measurements and Observations*: General health observations were made once daily throughout the study. Injection sites were visually evaluated at 2, 24, and 48 hours after injection. Abnormal injection sites continued to be evaluated approximately every 24 hours until the site no longer had visible or palpable swelling.

d. Analysis: The concentrations of tulathromycin in plasma were measured using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay validated for swine plasma. Pharmacokinetic parameters were determined for each individual animal.

Plasma concentrations and PK variables were analyzed using a general linear mixed model in SAS. Plasma concentrations, C_{max}, and $AUC_{0\text{-}LOQ}$ were log-transformed prior to analysis. The back-transformed least squares (LS) means and 90% confidence intervals (CI) were reported. Bioequivalence was assessed for C_{max} and $AUC_{0\text{-}LOQ}$. The bioequivalence criteria used was 70-143% for C_{max} and 80-125% for $AUC_{0\text{-}LOQ}$.

e. *Results*: The average PK profiles of DRAXXIN Injectable Solution and DRAXXIN 25 Injectable Solution in swine show overall similarity (Figure 1), as demonstrated statistically by comparable C_{max} and AUC values. The largest differences in plasma profiles are observed in the first 24-hour period after dosing.

Figure 1. Average concentration of tulathromycin in swine plasma when administered as a single IM injection at a dose of 2.5 mg/kg BW of either DRAXXIN Injectable Solution (reference; n = 32) or DRAXXIN 25 Injectable Solution (test; n = 30).



Summary statistics for PK parameters per treatment group are shown in Table 1. The results for DRAXXIN 25 Injectable Solution (test) only contain data from 30 animals because two pigs were removed due to unresolved lameness (not related to treatment). One pig was removed from the study after enrollment but before treatment, and another pig was removed after the treatment commenced.

Table 1. A summary of PK parameter statistics (n = 32 for reference; n = 30 for test) and standard deviations per treatment (average ± SD) following the administration of DRAXXIN Injectable Solution (reference) and DRAXXIN 25 Injectable Solution (test) in swine as a single IM injection of 2.5 mg tulathromycin/kg BW.

PK Parameter	DRAXXIN Injectable Solution (reference)	DRAXXIN 25 Injectable Solution (test)
C_{max} (ng/mL)	551 ± 148	450 ± 121
$AUC_{0\text{-}LOQ}$ (h*ng/mL)	8134 ± 1318	8227 ± 1166
$AUC_{0\text{-}inf}$ (h*ng/mL)	8664 ± 1357	8610 ± 1203
T_{max} (h)	0.382 ± 0.121	0.669 ± 0.639
$T_{½}$ (h)	70.1 ± 25.2	67.7 ± 16.0

C_{max} - maximum plasma concentration
$AUC_{0\text{-}LOQ}$ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay
$AUC_{0\text{-}inf}$ - the area under the plasma concentration vs. time curve from time of injection extrapolated to infinity
T_{max} - the time after initial injection to when C_{max} occurs
$T_{½}$ - the plasma elimination half-life of tulathromycin

The ratio of the means between DRAXXIN Injectable Solution (100 mg/mL) and DRAXXIN 25 Injectable Solution (25 mg/mL) was contained within the 90% confidence limits of 0.70 – 1.43 for C_{max} and 0.80 – 1.25 for $AUC_{0\text{-}LOQ}$ (Table 2). These results indicate that the two products have comparable pharmacokinetic characteristics and are considered pharmacologically equivalent.

Table 2. Back-transformed least squares (LS) means and 90% confidence intervals (CI) for C_{max} and $AUC_{0\text{-}LOQ}$ following a single IM injection of 2.5 mg tulathromycin/kg BW in swine administered as DRAXXIN Injectable Solution (reference) and DRAXXIN 25 Injectable Solution (test).

PK Parameter	LS Mean DRAXXIN Injectable Solution (Reference)	LS Mean DRAXXIN 25 Injectable Solution (Test)	Ratio % Reference	90% CI
$AUC_{0\text{-}LOQ}$ (h*ng/mL)	8033	8144	1.01	0.95 - 1.08
C_{max} (ng/mL)	532	437	0.82	0.74 – 0.92

f. Adverse Events: Two animals receiving DRAXXIN 25 Injectable Solution had measurable injection site swelling at 2 hours post-injection. By 24 hours only one animal had measurable swelling at the injection site, which resolved by five days post-injection. No animals receiving DRAXXIN Injectable Solution had measurable injection site swelling. Except for these injection site reactions, no other treatment-related adverse reactions were reported.

g. Conclusion: Based on the statistical comparison of C_{max} and $AUC_{0\text{-}LOQ}$ between the groups, DRAXXIN 25 Injectable Solution is pharmacologically equivalent to DRAXXIN Injectable Solution (NADA 141-244) when administered to swine once by IM injection at a dose of 2.5 mg tulathromycin/kg BW. Therefore, DRAXXIN 25 Injectable Solution is effective 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, when administered to swine once by IM injection at a dose of 2.5 mg tulathromycin/kg BW.

III. TARGET ANIMAL SAFETY:

A. Systemic Safety

Evaluation of target animal safety in swine was based on a PK comparison between the new tulathromycin formulation (DRAXXIN 25 Injectable Solution) and DRAXXIN Injectable Solution. Tulathromycin administered to swine as DRAXXIN 25 Injectable Solution at a dose of 2.5 mg tulathromycin/kg BW once by IM injection was demonstrated to be pharmacologically equivalent to a corresponding IM injection of DRAXXIN Injectable Solution based upon comparability of their respective $AUC_{0\text{-}LOQ}$ and C_{max} values (see EFFECTIVENESS section above). Because of the demonstrated blood-level pharmacologic equivalence, this study confirms the systemic safety of DRAXXIN 25 Injectable Solution in swine when administered by IM injection at a dose of 2.5 mg tulathromycin/kg BW once.

The FOI Summary for the approval of DRAXXIN Injectable Solution, NADA 141-244, dated May 24, 2005, contains the results of the systemic target animal safety study confirming the safety of tulathromycin when administered to swine by IM injection at a dose of 2.5 mg tulathromycin/kg BW once.

B. Injection Site Safety

1. Title: Injection Site Tolerance DRAXXIN Lower Concentration (DRAXXIN 25) in Swine (study #1423N-60-11-389; August 2011 to July 2012).

2. Study Director: Devendra Kumar, B.V.Sc. & A.H., M.S., Ph.D., Pfizer Animal Health, Richland, MI.

3. Study Design:

   a. *Objective*: To characterize the injection site tolerance of DRAXXIN 25 Injectable Solution for Swine when injected intramuscularly to growing pigs once at the maximum proposed dose volume of 4 mL per injection site or at the dose rate of 2.5 mg/kg BW, whichever was higher.

   b. *Animals*: Sixteen healthy, commercial crossbred, castrated male and female, swine, weighing 22.5 to 26.5 kg at arrival, were enrolled in the study. Animals were housed individually in pens, and were randomly assigned to pen, treatment group, and necropsy day.

c. *Test Article Administration*: The test article was tulathromycin as DRAXXIN 25 Injectable Solution (25 mg tulathromycin/mL). The control article was sterile saline injectable solution. Pigs were injected intramuscularly with 4 mL or 2.5 mg tulathromycin/kg BW (whichever resulted in a higher volume per injection site) once in the neck. The calculated dose volume was less than 4 mL for all the pigs in the study. Therefore, all pigs received 4 mL of either DRAXXIN 25 Injectable Solution or saline by IM injection in the neck on Day 0.

d. *Measurements and Observations*: General health observations were conducted by trained personnel on all animals at least once daily from Day -14 until the last day of the study (Day 42). Clinical observations were conducted by the study veterinarian at least once on Days -14, -1, 0, 7, 14, 28, and 42. Two saline-treated pigs and two DRAXXIN 25 Injectable Solution-treated pigs were euthanized on Days 7, 14, 28, and 42.

4. Statistical Analysis: None.

5. Results:

a. *General Health and Clinical Observations*: There were no abnormal clinical observations or general health observations related to test article administration. All treated animals completed the study.

b. *Injection Site Observations*: Injection site observations revealed no findings of heat, sensitivity, necrosis, firmness, swelling, or drainage at any of the injection sites in either treatment group. Erythema was observed in two DRAXXIN 25 Injectable Solution-treated pigs on Day 1.

c. *Gross Necropsy and Histopathology*: Gross necropsy observations revealed discoloration in injection sites in both DRAXXIN 25 Injectable Solution-treated pigs necropsied on Day 7, in both DRAXXIN 25 Injectable Solution-treated pigs necropsied on Day 14, and in one saline-treated pig necropsied on Day 14. The discoloration was described as either tan, red, and light brown; tan and red; tan; or tan, brown, and dark red mottled. No grossly visible changes were observed for saline-treated pigs at any time period except for one pig necropsied on Day 14. No grossly visible changes were observed for DRAXXIN 25 Injectable Solution-treated pigs on Days 28 and 42.

Microscopic changes consistent with inflammation were seen in seven saline-treated pigs and in six DRAXXIN 25 Injectable Solution-treated pigs. The changes in DRAXXIN 25 Injectable Solution-treated pigs were more commonly graded mild to moderate than the changes in saline-treated pigs, which generally received grades of minimal to mild. No microscopic findings were observed in the DRAXXIN 25 Injectable Solution-treated pigs necropsied on Day 42 of the study.

6. Conclusion: This study demonstrated that DRAXXIN 25 Injectable Solution was well tolerated when injected intramuscularly in growing pigs at the maximum labeled dose volume of 4 mL per injection site. Injection site irritation (as evidenced by grossly visible lesions at necropsy) extended beyond the assigned pre-slaughter withdrawal period.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

Information on the impact of the change in concentration from 100 mg/ml to 25 mg/ml was not required for this approval, because the product was determined to be bioequivalent to the approved product, and no changes in use patterns are anticipated with this approval.

Decision Statement:

CVM did not require additional information for antimicrobial resistance considerations associated with this new formulation. The FOI Summaries for 1) the original approval of NADA 141-244, dated May 24, 2005, and 2) a supplemental approval dated September 8, 2009, contain a summary of all information used to assess the antimicrobial resistance risks and their mitigation(s).

B. Impact of Residues on Human Intestinal Flora:

Decision Statement:

CVM did not require additional information for microbial food safety (antimicrobial resistance) for this approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of all information used to assess the impact of residues on human intestinal flora.

C. Toxicology:

No reassessment of the toxicological ADI was needed for this approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of all toxicology studies and information.

D. Assignment of the Final ADI:

The final ADI is the toxicological ADI of 15 µg/kg body weight (BW)/day derived from the development toxicity study in rats. The NOEL from this study was 15 mg/kg BW/day. Based on this study and a safety factor of 1,000, the ADI is 15 µg/kg BW/day (21 CFR 556.745).

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

The safe concentration of total tulathromycin residues in each edible tissue of swine is 3 ppm for muscle, 9 ppm for liver, 18 ppm for kidney, and 18 ppm for fat.

F. Residue Chemistry:

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      CVM did not require total residue and metabolism studies for this approval. The FOI Summary for the original approval of NADA 141-244 dated

May 24, 2005, contains summaries of total residue and metabolism studies for tulathromycin in swine.

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of comparative metabolism studies for tulathromycin in swine.

c. Tissue Residue Depletion Study

(1) The bioequivalence Study No. 1522N-60-11-382 (Section IIB, above) provides information on the plasma concentrations of the marker residue in DRAXXIN 25 (tulathromycin) Injectable Solution and DRAXXIN Injectable Solution at sampling time points up to 12 days. These data confirm that the 5-day tissue withdrawal period established for the original approval is appropriate for this approval.

(2) Study Title – "Determination of the Concentration of Tulathromycin Residues (CP-60,300) in Injection Site and Edible Tissues of Swine Receiving One Intramuscular Injection of DRAXXIN (25 mg/ml) at 2.5 mg/kg Bodyweight" Study No. 1521N-60-11-376.

Study Director: Michael E. Guyton, Zoetis, Kalamazoo, MI

Animals Species: Crossbred swine

Number of Animals/Sex: 36, 18 males, 18 females (no control animals)

Weights of Animals: 42 to 51 kg

Health Status: Healthy

Route of Administration: Intramuscular (IM) injection

Dose Rate: 2.5 mg/kg body weight (BW)

Duration of Dosing: Once

The concentration of tulathromycin and tulathromycin-related residues, measured as the marker residue, CP-60,300, was determined in the kidney (target tissue), injection site muscle, liver and fat of treated swine. Samples were assayed by a validated LC-MS/MS procedure. These data, in tabular form, are presented in Table 3.

Table 3. Mean residue concentrations (ppb) in kidney, injection site muscle, surrounding injection site muscle, liver, and fat tissue samples (Study No. 1521N-60-11-376).

Withdrawal Time (days)	Mean Tulathromycin Residues in Kidney (ppb ± SD)	Tulathromycin Residues in Injection Site Muscle (ppb ± SD)	Tulathromycin Residues in Muscle (ppb ± SD)	Tulathromycin Residues in Liver (ppb ± SD)	Tulathromycin Residues in Fat (ppb ± SD)
10 to 12 hours	4,421 ± 736	38,625 ± 15,747	1,227 ± 247	1,288 ± 185	423 ± 151
2	5,218 ± 936	4,860 ± 525	1,076 ± 39	2,121 ± 200	455 ± 98
4	3,485 ± 962	4,843 ± 878	681 ± 73	2,335 ± 310	277 ± 79
7	2,074 ± 161	2,658 ± 698	344 ± 20	1,709 ± 261	169 ± 30
14	1,040 ± 202	1,193 ± 124	145 ± 42	969 ± 189	46 ± 1.9
21	484 ± 69	826 ± 414	60 ± 14	499 ± 54	18 ± 3
28	353 ± 79	704 ± 112	38 ± 15	202 ± 55	NA
35	169 ± 33	314 ± 57	15 ± 2	112 ± 30	NA
42	115 ± 11	276 ± 144	13 ± 4	46 ± 14	NA
LOQ (ppb)	193	88	88	104	93
LOD (ppb)	59	27	27	32	28

NA Sample not analyzed

Using the residue depletion data from Study Number 1521N-60-11-376, the tolerance of 15 ppm (15,000 µg/kg) for the marker residue (common fragment, CP-60,300) in the target tissue (kidney) and a statistical algorithm that determines the upper 95% confidence limits on the 99th percentile for kidney residues, a 1-day withdrawal period is calculated.

2. Target Tissue and Marker Residue

No reassessment of target tissue and marker residue was needed for this approval. The FOI Summary for the original approval of NADA 141-244 dated May 24, 2005, contains a summary of information used to determine kidney as the target tissue and CP-60,300 as the marker residue for swine.

3. Tolerances

The tolerance for CP-60,300 (the marker residue) is 15 ppm in swine kidney (21 CFR 556.745) (NADA 141-244).

4. Withdrawal Period and Milk Discard Time

A 5-day withdrawal period is assigned for the tulathromycin 25 mg/mL product. The results of the bioequivalence study support a 5-day withdrawal period and a 5-day withdrawal period also is assigned for the approved tulathromycin 100 mg/mL product. Assigning a 5-day withdrawal period to the tulathromycin 25 mg/ml product provides consistency across the tulathromycin products for use in swine.

G. Analytical Method for Residues:

1. Description of Analytical Method

The method for determination of tulathromycin in swine kidney is a modified version of the regulatory LC-MS/MS assay described in the FOI Summary for the original approval of NADA 141-244 dated May 24, 2005. The modified method uses automated SPE clean-up in place of the manual SPE of the regulatory method. The modified method also makes use of calibration standards prepared in extracted blank matrix, instead of the solvent standards used in the regulatory method. The confirmatory procedures are identical to those of the regulatory method described in the FOI Summary for the original approval of NADA 141-244 dated May 24, 2005.

2. Availability of the Method

The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 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 25 Injectable Solution:

WARNINGS
FOR USE IN ANIMALS ONLY.
NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.

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 25 Injectable Solution, when used according to the label, is safe and effective 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. Additionally, data demonstrate that residues in food products derived from species treated with DRAXXIN 25 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). Adequate directions for lay use cannot be written because (a) professional expertise is required to appropriately diagnose and subsequently use this product to treat and control SRD 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)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

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