Date of Approval: June 1, 2021

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-543

Draxxin® KP

tulathromycin and ketoprofen injection

Injectable solution

Beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers

For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD

Sponsored by:

Zoetis Inc.

Executive Summary

Draxxin® KP (tulathromycin and ketoprofen injection) is approved for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers. Draxxin® KP is not for use in reproducing animals over one year of age, dairy calves, or veal calves.

Tulathromycin is a macrolide antibiotic, and as a class, macrolides tend to be mainly bacteriostatic but may be bactericidal against some pathogens. Macrolides also tend to show concentration-independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration. Tulathromycin has shown *in vitro* activity against the four pathogens associated with BRD that are listed on the label for Draxxin® KP.

Ketoprofen is in the propionic acid class of non-narcotic, nonsteroidal anti-inflammatory drugs (NSAIDs) and has characteristic antipyretic activity. Like many NSAIDs, ketoprofen works by inhibiting the enzyme cyclooxygenase, which in turn leads to decreased synthesis of prostaglandins. Prostaglandins are present throughout the body and contribute to signs of inflammation, such as fever. Prostaglandins have other important functions, such as protecting the lining of the gastrointestinal tract, helping to maintain blood flow to the kidneys, and supporting platelet function.

Proprietary Name	Established Name	Dosage Form	Application Type and Number	Sponsor
Draxxin® KP	tulathromycin and ketoprofen injection	Injectable Solution	New Animal Drug Application (NADA) 141-543	Zoetis Inc.

Safety and Effectiveness

The sponsor conducted a multi-site, natural infection, field study to show that Draxxin® KP treats BRD and controls pyrexia associated with the disease. The study included crossbred beef calves sourced from multiple livestock auctions that were at high risk for developing BRD. Cattle were enrolled if they had clinical signs of BRD, including defined levels of depression and respiratory distress as well as a fever of at least 104.5 °F. Cattle were given a single subcutaneous dose of one of the following: (1) Draxxin® KP; (2) Draxxin® (which contains tulathromycin alone and is approved under NADA 141-244); or (3) saline. The effectiveness of the combination drug was compared to the effectiveness of saline alone and tulathromycin alone (as Draxxin®).

An animal was considered a treatment success for the treatment of BRD if it remained in the study until Day 14 (i.e., was not removed from the study as a treatment failure between Days 3 to 13), and had improved clinical signs and a rectal temperature less than 104.5 °F on Day 14. An animal was considered a treatment success for the control of pyrexia if its rectal temperature was at least 2 °F lower 6 hours after treatment compared to its rectal temperature at enrollment.

Compared to the saline group, significantly more cattle in the Draxxin® KP group were treatment successes for both the treatment of BRD and control of pyrexia. Compared to the Draxxin® group, significantly more cattle in the Draxxin® KP group were treatment successes for the control of pyrexia. The Draxxin® KP group also was statistically non-inferior to the Draxxin® group for the treatment of BRD, meaning the combination drug was as good as tulathromycin at treating the disease. For the microbiology assessment, at least 30 isolates of each pathogen listed on the label for Draxxin® KP were identified from at least 30 animals across the study. No adverse reactions related to the drug were seen in the study.

The sponsor conducted a safety study in growing male and female beef calves. The calves were dosed subcutaneously at 0X, 1X, 3X, or 5X the recommended dose of Draxxin® KP every 14 days for a total of 3 injections. Overall, Draxxin® KP was well-tolerated in all treatment groups. There were higher absolute and relative numbers of segmented neutrophils in the 1X, 3X, and 5X groups at various timepoints throughout the study. This may be secondary to injection site inflammation caused by the drug. The 1X, 3X, and 5X groups also had higher creatine kinase values, which were directly associated with injection site reactions. One calf in the 5X group was positive for fecal occult blood on two days of the study; however, this calf did not have any correlating gross pathology or microscopic lesions at necropsy. Microscopic mucosal erosions of the pyloric region of the abomasum were considered related to Draxxin® KP. These adverse effects on the gastrointestinal tract were expected based on the mechanism of action of the ketoprofen component of the combination drug. The label instructs veterinarians to stop giving Draxxin® KP if fecal blood is observed and to not use the drug in cattle that are dehydrated or with known kidney disease.

The sponsor did not conduct safety studies in pregnant or lactating cattle, in cattle of reproductive age intended for breeding, or in calves less than 2 months of age. Therefore, the label states that Draxxin® KP is not for use in reproducing animals over one year of age, dairy calves, or veal calves.

Human Food Safety

The FOI Summaries for the original approval of tulathromycin (as Draxxin®), dated May 24, 2005, under NADA 141-244, and the supplemental approval of ketoprofen (as KETOFEN®), dated May 25, 2021, under NADA 140-269, contain summaries of the information used to assess human food safety for KETOFEN®.

FDA determined that the sponsor did not need to develop or submit for review additional data to address the use of tulathromycin in combination with ketoprofen in cattle on microbial food safety (antimicrobial resistance).

FDA also determined that it was not necessary to reassess the acceptable daily intake and safe concentrations for tulathromycin and ketoprofen or the acute reference dose for ketoprofen. The potential for tulathromycin and ketoprofen residues to interact and cause increased toxicity is not a concern because the elimination half-life of ketoprofen in cattle is much shorter than the established tissue withdrawal period for Draxxin® KP.

For tulathromycin, the target tissue is liver and the marker residue is CP-60,300. For ketoprofen, the target tissue is kidney and the marker residue is ketoprofen. FDA previously established the tolerances for both components of the combination drug. The sponsor conducted 1 residue depletion study to establish the tissue withdrawal period for the combination drug in cattle. FDA used the information from this study, along with data from the previous approvals of each component, to establish a tissue withdrawal period of 18 days for Draxxin® KP.

Draxxin® KP is not for use in lactating cattle or calves less than 2 months of age; therefore, a milk discard time was not established and a tissue withdrawal period was not established in pre-ruminating calves.

Conclusions

Based on the data submitted by the sponsor for the approval of Draxxin® KP, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

NADA 141-543

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Draxxin® KP

D. Drug Product Established Name

tulathromycin and ketoprofen injection

E. Pharmacological Category

Antimicrobial and non-steroidal anti-inflammatory

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

100 mg/mL tulathromycin and 120 mg/mL ketoprofen

H. How Supplied

50 mL, 100 mL, 250 mL, and 500 mL multiple dose bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg tulathromycin and 3 mg ketoprofen/kg (1.1 mL/100 lb) bodyweight.

K. Route of Administration

Subcutaneous

L. Species/Class

Cattle: beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers. Not for use in reproducing animals over one year of age, dairy calves, or veal calves.

M. Indication

Draxxin® KP is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers. Not for use in reproducing animals over one year of age, dairy calves, or veal calves.

II. EFFECTIVENESS

FDA concluded that Draxxin® KP is effective for the labeled indications. The effectiveness of Draxxin® KP was demonstrated in one well-controlled, multi-site, natural infection field study. Draxxin® KP was administered to 273 crossbred beef steers, heifers, and bulls. The effectiveness of Draxxin® KP was compared both to saline alone (using a superiority test for both indications) and to tulathromycin alone (using a non-inferiority test for treatment of BRD and a superiority test for control of pyrexia associated with BRD). The most common adverse reaction seen was lameness, which was not considered to be test article-related because it occurred at a very low incidence (9 of 819 study animals) and was seen in treated and control animals.

A. Dosage Characterization

The dosage of Draxxin® KP for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD was selected based on the approved doses of the individual drugs for these indications in cattle. Tulathromycin is approved as Draxxin® (NADA 141-244) for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* when administered as a single subcutaneous (SC) injection of 2.5 mg/kg body weight (bw). Ketoprofen is approved as Ketofen® (NADA 140-269) for the control of pyrexia associated with BRD when administered as a single SC injection of 3 mg/kg bw.

B. Substantial Evidence

1. Natural Infection Field Study

Title: A Tulathromycin-Ketoprofen Combination Indicated for the Treatment of BRD Associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, and Control of BRD-associated Pyrexia in Steers, Beef Heifers, Beef Bulls, Dairy Bulls and Dairy Replacement Heifers. (Study No. A131C-US-17-531)

Study Dates: September 2017 to December 2018

Study Locations: Reedley, CA; Oakland, NE (2 sites); Eden, ID; and Parma, ID

Study Design:

Objective: To demonstrate the effectiveness of Draxxin® KP (tulathromycin and ketoprofen injection) for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*, and control of pyrexia associated with BRD.

Study Animals: A total of 819 animals were enrolled across five U.S. study sites in Nebraska, Idaho, and California. The study animals were crossbred beef, mixed sex (steers, bulls, and heifers) animals weighing 149 to 325 kg, approximately 5 to 12 months of age, and were sourced from multiple livestock auctions. Study animals were housed in outdoor dirt-floored pens typical of U.S. and commercial design in terms of pen size, pen density, and bunk space. Feed rations complied with or exceeded NRC recommendations. Animals had *ad libitum* access to water.

Experimental Design: This was a multi-site, randomized, masked field effectiveness study. Animals meeting the BRD inclusion criteria (described below) were randomly assigned to one of three treatment groups – Draxxin® KP (tulathromycin and ketoprofen injection, T03), tulathromycin alone (T02), or saline (T01). Animals were allocated to treatments according to a randomized complete block design based on order of treatment administration and a randomization schedule replicated at each study site. Up to four consecutive blocks (3 to 12 animals) enrolled on the same day were housed together in each pen; pens were filled consecutively as animals were enrolled. A total of 273 animals (53 to 55 per site) were enrolled in each treatment group. The individual animal was the experimental unit. Only treatment administration personnel had access to treatment records during the study. All other personnel involved in the conduct of the study were masked to treatment assignments until the end of the animal phase of the study. The study was conducted in accordance with Good Clinical Practice guidelines.

Drug Administration: Animals were administered either 1) Draxxin® KP (tulathromycin and ketoprofen injection) containing 100 mg tulathromycin and 120 mg ketoprofen per mL, administered once at 2.5 mg tulathromycin/kg bw and 3 mg/kg ketoprofen/kg bw, or 2) commercially available Draxxin® (tulathromycin) sterile solution containing 100 mg

tulathromycin per mL, administered once at 2.5 mg tulathromycin/kg bw, or 3) commercially available 0.9% sterile saline solution administered once at 0.025 mL/kg bw. All assigned treatments were administered by SC injection in the neck on the day of enrollment (Day 0).

Measurements and Observations: General health observations were conducted and recorded daily beginning on day of arrival and continued through Day 14 (end of study). When sufficient numbers of animals (based on the judgement of the investigator) were displaying signs of BRD to begin enrollment, animals that met clinical score inclusion criteria (respiratory score of ≥2 on a scale from 0 [normal] to 3 [severe respiratory distress], and an attitude score of ≥2 on a scale from 0 [normal] to 4 [moribund]) were sorted into a chute, weighed, and had their rectal temperature measured. Animals that met the clinical score criteria and had a rectal temperature of ≥104.5 °F were enrolled, administered their assigned treatment, and placed in their assigned pens. A double-guarded nasopharyngeal swab was collected from each animal immediately prior to enrollment for bacterial isolation.

Clinical scores (respiratory and attitude score) were recorded approximately 6 hours post-treatment, and on Days 1 through 14. Rectal temperatures were recorded for each animal approximately 6 hours post-treatment, on Days 3-13 for animals with respiratory or attitude score of "2", and for all remaining animals on Day 14. Animals meeting treatment failure criteria (described below) on Days 3-13 were removed and either given therapeutic intervention or euthanized. Lung swabs were taken from cattle that died or were euthanized during the study.

An animal was classified as a BRD treatment failure if at any time during Days 3-13 it had 1) a respiratory score of "2" and a rectal temperature ≥104.5 °F, 2) an attitude score of "2" and a rectal temperature ≥104.5 °F, 3) a respiratory score of "3" regardless of rectal temperature, 4) an attitude score of "3" regardless of rectal temperature, or 5) if it died due to BRD. Animals evaluated on Day 14 that did not meet the treatment success criteria were also considered BRD treatment failures.

The primary variables were BRD treatment success and treatment success for control of pyrexia:

> BRD Treatment Success: An animal was classified as a treatment success if it remained in the study until Day 14 and was not previously classified as a treatment failure, and on Day 14 had a respiratory score of ≤1, and an attitude score of ≤1, and a rectal temperature <104.5 °F.
>
> Treatment Success for Control of Pyrexia: An animal was classified as a treatment success if it had at least a 2 °F reduction in rectal temperature at 6 hours post-treatment compared to pre-treatment.

To be considered effective, all of the following criteria had to be met:

- the percentage of animals classified as a success (treatment success rate) for the treatment of BRD in the Draxxin® KP-treated group is

significantly different (P<0.05) and higher than the treatment success rate for the treatment of BRD in saline-treated animals on Day 14;
- the treatment success rate for pyrexia reduction at 6 hours post-treatment in the Draxxin® KP-treated group is significantly different (P<0.05) and numerically higher than the treatment success rate for pyrexia reduction at 6 hours post-treatment in the saline group;
- the treatment success rate for pyrexia reduction at 6 hours post-treatment in the Draxxin® KP-treated group is significantly different (P<0.05) and numerically higher than the treatment success rate in the tulathromycin-treated group;
- there is statistical non-inferiority between the treatment success rates for the treatment of BRD in the Draxxin® KP-treated group compared to the tulathromycin-treated group on Day 14; and
- at least 30 isolates of each pathogen species (*M. haemolytica*, *P. multocida*, *H. somni*, and [optional] *M. bovis*) are identified from at least 30 study animals across the study.

Statistical Methods:

BRD Treatment Success: BRD treatment success was coded as a binary variable (1=yes, 0=no) and listed for each animal. Treatment success was analyzed using a generalized linear mixed model with binomial error distribution and logit link function. The model included fixed effect of treatment and random effects of site, treatment by site interaction and pen within site. Back-transformed estimates of success rate, 95% confidence intervals, and number of animals included in the analysis were reported for each treatment group. Comparisons were conducted for T03 vs. T01 and T03 vs. T02. Non-inferiority testing was conducted between T03 and T02 using a 1-sided, alpha=0.025 and a 15% non-inferiority margin. Non-inferiority of T03 to T02 was concluded if the lower limit of the 95% confidence interval on difference in success rates (T03-T02) was greater than -15%.

Treatment Success for Control of Pyrexia: For each animal, it was determined if at least a 2 °F reduction in rectal temperature at 6 hours post-treatment compared to baseline (1=yes, 0=no) was observed. This variable (pyrexia treatment success) was analyzed using a generalized linear mixed model with binomial error distribution and logit link function. The model included fixed effect of treatment and random effects of site, treatment by site interaction and pen within site. Back-transformed estimates of success rate, 95% confidence intervals and number of animals included in the analysis was reported for each treatment group. Comparisons were conducted for T03 vs. T01 and T03 vs. T02.

Results:

BRD Treatment Success: The back-transformed estimate for BRD treatment success was significantly different and numerically higher for the Draxxin® KP-treated group compared to the saline-treated group (76.2% [T03] vs 31.6% [T01], P=0.0020) and numerically higher than the tulathromycin-treated group (76.4% [T03] vs. 71.9% [T02]). In addition, the Draxxin® KP-treated group was shown to be statistically non-inferior compared to the

tulathromycin-treated group, with the lower limit of the 95% confidence interval on difference in success rates (T03-T02) being -6.0%.

Treatment Success for Control of Pyrexia: Substantial evidence of the effectiveness of the Draxxin® KP group (T03) for control of pyrexia associated with BRD was demonstrated by a significantly different and numerical increase in control of pyrexia associated with BRD (back-transformed estimate of pyrexia treatment success rate % and 95% confidence intervals) compared with the saline group [T01=2.4%, (0.4% to 12.1%) vs. T03=83.8%, (55.4% to 95.6%; P=0.0010)] at 6 hours post-dosing. Substantial evidence of the contribution of ketoprofen to the effectiveness of the Draxxin® KP-treated group (T03) was demonstrated by a significantly different and numerical increase in control of pyrexia associated with BRD (back-transformed estimate of pyrexia treatment success rate % and 95% confidence intervals) compared with the tulathromycin-treated group [T02=5.4%, (1.3% to 20.0%) vs. T03=83.9%, (57.2% to 95.3%); P=0.0032)] at 6 hours post-dosing.

Microbiology: *Mannheimia haemolytica* (N=504 positive samples), *Pasteurella multocida* (N=84 positive samples), *Histophilus somni* (N=114 positive samples), and *Mycoplasma bovis* (N=197 positive samples) were isolated from pre-enrollment deep nasopharyngeal swabs and/or lung swabs from animals during the study.

Adverse Reactions: There were no test article-related adverse events or unexplained deaths in this study. Lameness (9 animals across all groups), bloat (1 animal in T03), and submandibular edema (1 animal in T01) were observed in study animals. These conditions are not uncommon in feedlot cattle and are not known to be associated with the use of tulathromycin or ketoprofen in cattle; therefore, they were not considered related to test article administration.

Conclusion: This study demonstrates that Draxxin® KP (tulathromycin and ketoprofen injection) is effective for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*, and control of pyrexia associated with BRD in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and dairy replacement heifers, when administered at a dose of 2.5 mg tulathromycin/kg bw and 3 mg ketoprofen/kg bw by subcutaneous injection.

III. TARGET ANIMAL SAFETY

A pharmacokinetic (PK) study (Study Number A431N-US-16-418) was used to determine the dosing interval and duration of the margin of safety study A332N-US-17-569. Pharmacokinetic and simulation analyses of the individual animal concentration-time data supported a dosing interval of 14 days.

The safety of Draxxin® KP (tulathromycin and ketoprofen injection) in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and dairy replacement heifers (not for use in reproducing animals greater than one year of age), when administered at 2.5 mg tulathromycin/kg body weight (bw) and 3 mg

ketoprofen/kg bw [1.1 mL/100 lb bw] as a single subcutaneous injection was demonstrated in the following margin of safety study.

A. Type of Study: Margin of Safety

Title: Margin of Safety of Tulathromycin-Ketoprofen Combination in Cattle. (Study Number A332N-US-17-569)

Study Dates: October 2017 to November 2018

Study Location: Richland, MI

Study Design:

Objective: The objective of this study was to characterize the safety of a tulathromycin-ketoprofen combination when administered subcutaneously 3 times at 14-day intervals to cattle up to 5 times the maximum recommended dose. The recommended dose of the combination drug product was 2.5 mg/kg tulathromycin and 3 mg/kg ketoprofen as a single subcutaneous injection.

Study Animals: 32 growing beef cattle (16 male, 16 female), 5 to 7 months of age, 4 animals per sex per treatment group, and weighing 239-321 kg body weight.

Experimental Design: The study was a masked, randomized, margin of safety study with a negative control. Within each sex, animals were assigned to one of four treatments (0X, 1X, 3X, and 5X) completely at random. Animals were randomized to pens and to treatments or replacement order on Day -14 (± 1 day). The study included a 30-day acclimation period Treatments were administered on Days 0, 14, and 28. Animals were housed individually. Study personnel making evaluations were masked to treatment. Animals were necropsied on Day 32/33 by a board-certified pathologist. The pathologist was masked for necropsies and gross pathology evaluations, but unmasked during the histopathology evaluations. This study was conducted in compliance with Good Laboratory Practice (GLP) Regulations (21 CFR Part 58).

Drug Administration: Animals received saline or tulathromycin and ketoprofen injection via subcutaneous injection at three different sites in the neck according to the table below.

Table III.1 Treatment Groups

Group	Treatment	Dosing Regimen	Number of Animals
T01 (0X)	Saline (0.125 mL/kg bw)	3 Subcutaneous Injections (On Days 0, 14, and 28)	8 (4M/4F)
T02 (1X)	2.5 mg/kg bw tulathromycin and 3.0 mg/kg bw ketoprofen (0.025 mL/kg bw)	3 Subcutaneous Injections (On Days 0, 14, and 28)	8 (4M/4F)
T03 (3X)	7.5 mg/kg bw tulathromycin and 9.0 mg/kg bw ketoprofen (0.075 mL/kg bw)	3 Subcutaneous Injections (On Days 0, 14, and 28)	8 (4M/4F)
T04 (5X)	12.5 mg/kg bw tulathromycin and 15.0 mg/kg bw ketoprofen (0.125 mL/kg bw)	3 Subcutaneous Injections (On Days 0, 14, and 28)	8 (4M/4F)

Measurements and Observations: Clinical Observations (CO) consisted of visual evaluation of ocular, neurologic, respiratory, gastrointestinal, cardiovascular, lymphatic, musculoskeletal (including gait), integumentary, reproductive, feces and urinary systems as well as any other clinical observations. Physical Examinations (PE) consisted of a CO in addition to the measurement of temperature, heart rate and respiratory rate. The CO were conducted on Day -14 and once daily from Day -7 until Day 32/22. CO included a physical examination on Days -14, -7, -1, 1, 13, 15, 27, 29, and prior to necropsy (Day 32/33). On days of dosing, CO were performed and recorded before dose administration and at least 5 hours apart from daily General Health Observations (GHO). The GHO were conducted at least once daily throughout the study, starting on Day -14. The GHO included evaluation for changes in attitude, appetite, water consumption, ambulation, fecal consistency and color, and respiration (including rate and character). Animals were also evaluated for changes in skin condition, ocular discharge and function, nasal discharge, and oral discharge. Limbs were evaluated for signs of swelling and changes in hoof conformation.

Comprehensive injection site evaluations [redness, heat, sensitivity, hardness, and volume of swelling (calculated)] were conducted on all animals (at least once on Day -14, -7, and once daily from Day -1 until Day 32/33) at the same time as the CO. Prior to injection, the location for the injection site was shaved to facilitate observation of injection sites. On days of treatment administration (Days 0, 14, 28), injection site observations occurred before injections were given.

Body weights were recorded on Day -29, Day -7, before dosing on Days 0, 14, 28, and prior to necropsy (Day 32/33). Individual animal feed and water consumption was recorded daily beginning on Day -7.

Clinical pathology samples were collected for hematology, coagulation, and serum chemistry on Days -14, -7, -1, 1, 13, 15, 27, 29 and prior to necropsy (Day 32/33). Fecal samples were collected on Days -14, -8, -1, 1, 13, 15, 27, 29 and prior to necropsy (Day 32/33). Urine samples were collected on Days -15, -8, -1, 1, 13, 15, 27, 29 and at necropsy (Day 32/33). Plasma samples for

pharmacokinetics were collected on Days 0, 14, and 28: Pre-dose, 2.5 hours (+/- 10 mins) post-dose, 6 hours (+/- 15 mins) post-dose, 24 hours (+/- 30 mins) post-dose, 48 (+/- 60 mins) post dose, 96 hours (+/- 60 mins) post-dose, and 168 hours (+/- 120 mins; first 2 doses only) post-dose.

Statistical Methods:

The experimental unit was the individual animal.

Post-treatment body weight and numerical clinical pathology data were analyzed using a general linear mixed model for repeated measures. The model included fixed effects of treatment, time, sex, and all interactions among these effects. Random effects included the animal term and error. Where appropriate, a baseline covariate was included in the model. Post-treatment average daily feed and water consumption were computed for each animal and summarized using descriptive statistics (mean, standard deviation, minimum and maximum) by treatment, and by treatment and sex. Numerically recorded clinical pathology data (hematology, serum chemistry, coagulation, and urinalysis) were summarized indicating values that were outside the reference range.

Dose proportionality was assessed by visual inspection of plots of dose-normalized area under the drug concentration-time curve between times 0 and the last quantifiable concentration (AUC0-t(last)) and maximum plasma concentration (Cmax), and by analysis of variance comparing dose normalized (AUC0-t(last)) among the different groups. Drug accumulation was analyzed by comparing the AUC between times 0 and 96 hours post dose (AUC0-96 h), between the first and last doses.

Results: Cattle treated with tulathromycin and ketoprofen injection did not have clinically significant changes in body weight, feed or water consumption, or general health when compared to saline controls. There were no test article-related effects in the urinalysis.

There were higher absolute and relative numbers of segmented neutrophils in all test article treated groups at various timepoints throughout the study. Differences were of small magnitude, there was an absence of a dose response, and individual animals in all groups (treated and control groups) had values higher than normal prior to Day 0. Test article-related differences in serum chemistry parameters were lower alkaline phosphatase in the T04 group; lower albumin in the T03 and T04 groups; lower total protein (TP) and serum calcium in the T02, T03, and T04 groups; and higher creatine kinase (CK) in the T02, T03, and T04 groups. The changes for serum calcium and albumin were considered clinically insignificant because all values were within the normal reference range on the days with statistical differences. The changes for TP were considered secondary to the differences in albumin and clinically insignificant because the albumin changes were considered clinically insignificant. In addition, the only TP values that were outside of the normal reference range were only 0.1 g/dL below the normal reference range. The differences in neutrophil might be secondary to test article-associated injection site inflammation and the differences in CK values are directly associated with injection site reactions. A single calf in 5X group had

positive fecal occult blood samples on Days 15 and 29; however, this animal did not have any correlating gross pathology or microscopic lesions.

Microscopic mucosal erosions of the pylorus of the abomasum in T03 (2/8) and T04 (1/8) were considered test article-related. Injection site lesions evaluated microscopically contained edema, accumulation of fibrin, neutrophilic and/or mononuclear cell infiltration, granulomatous inflammation, fibrosis, hemorrhage, necrosis of adipose tissue in the subcutis, and/or fibrin thrombi within capillaries. Fibroplasia, hemorrhage, and mixed inflammation extended into the external musculature in some of the collected lesions. Microscopic injection site lesion incidence and severity was similar among treated groups. Renal interstitial inflammation and minimal multifocal degeneration and regeneration occurred at similar incidence and severity in treated and control calves and was considered unrelated to test article administration.

There were non-quantifiable ketoprofen plasma concentrations prior to the second and third doses, while there was a modest accumulation for tulathromycin (mean ≤16.5%) with the 14-day dosing interval. With an increase in dose from 1X to 5X, there was dose proportional increase in tulathromycin AUC0-t(last), while there was slightly greater than dose proportional increase in ketoprofen AUC0-t(last).

Conclusion: The study demonstrates that Draxxin® KP (tulathromycin and ketoprofen injection) is safe for use in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and dairy replacement heifers, when administered at 2.5 mg tulathromycin/kg body weight (bw) and 3 mg ketoprofen/kg bw [1.1 mL/100 lb bw] as a single subcutaneous injection.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

Tulathromycin was previously evaluated for its impact on microbial food safety - see FOI Summary for NADA 141-244 dated May 24, 2005. The Agency considered its combination with ketoprofen and does not think tulathromycin's impact on microbial food safety will be different as a result of this combination under the labeled conditions of use.

Ketoprofen is not an antimicrobial drug; therefore, no microbial food safety (antimicrobial resistance) was required.

Decision Statement:

Microbial food safety associated with the use of tulathromycin should not be affected by its inclusion in combination with ketoprofen under labeled conditions of use in cattle; therefore, no additional microbial food safety information or data was required.

B. Toxicology

<u>Tulathromycin</u>

Reassessment of the acceptable daily intake (ADI) or safe concentrations for tulathromycin was not 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 for tulathromycin.

The codified ADI for total residues of tulathromycin is 15 µg/kg bw/day, as listed in 21 CFR 556.745. The safe concentrations for total residues of tulathromycin in individual edible tissues of cattle are 3 parts per million (ppm) for muscle, 9 ppm for liver, 18 ppm for kidney, and 18 ppm for fat.

Ketoprofen

Reassessment of the ADI, acute reference dose (ARfD), or safe concentrations for ketoprofen was not needed for this approval. The FOI Summary for the supplemental approval of NADA 140-269, dated May 25, 2021, contains a summary of all toxicology studies and information for ketoprofen.

The ADI for total residues of ketoprofen is 5 µg/kg bw/day, as listed in 21 CFR 556.345. The safe concentrations for total residue of ketoprofen in the individual edible tissues of cattle are 0.25 ppm for muscle, 0.75 ppm for liver, 1.5 ppm for kidney, 1.5 ppm for fat, and 0.15 ppm for milk. These values reflect the partition of the ADI between meat (25% of the ADI) and milk (75% of the ADI).

The ARfD for total residue of ketoprofen is 20 µg/kg bw. The safe concentration for the muscle injection site is 4.0 ppm.

The potential for toxicity enhancement between tulathromycin and ketoprofen residues is of no concern to human consumers of food animals receiving treatment with this combination drug due to the fact that the ketoprofen elimination half-life in cattle is 0.5 to 1 hours, much shorter than the 18-day withdrawal period assigned for the use of Draxxin® KP.

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      Total residue and metabolism studies were not required for this approval. The FOI Summaries for the original approval of NADA 141-244, dated May 24, 2005, and the supplemental approval of NADA 140-269, dated May 25, 2021, contain a summary of total residue and metabolism studies for tulathromycin and ketoprofen, respectively, in cattle.

   b. Comparative Metabolism Study

      CVM did not require comparative metabolism studies for this approval. The FOI Summaries for the original approval of NADA 141-244, dated May 24, 2005, and the supplemental approval of NADA 140-269, dated

May 25, 2021, contain a summary of comparative metabolism studies for tulathromycin and ketoprofen, respectively, in cattle.

c. Study to Establish Withdrawal Period

(1) Tissue Residue Depletion Study

Title: Pivotal Tissue Residue Decline Study in Beef Cattle Receiving a Single Subcutaneous Dose of a Combination Product Containing Ketoprofen and Tulathromycin at a Dose Rate of 3 mg/kg Body Weight Ketoprofen and 2.5 mg/kg Body Weight Tulathromycin. (Study Number A433N-US-18-615)

Study Dates: July 2, 2018, to April 19, 2019

Study Locations: Tulare, CA, and Kalamazoo, MI

Study Design: Thirty-six (18 steers and 18 heifers) black and red angus cattle, weighing 394 to 492 kg on Study Day -1, were treated with a single subcutaneous injection containing 3 mg ketoprofen/kg bw and 2.5 mg tulathromycin/kg bw. Animals were slaughtered at either 1, 4, 7, 12, 18, 24, 30, or 36 days post-dose. Muscle, liver, peri-renal fat, kidneys, and injection site (core and ring samples) were collected and analyzed for ketoprofen and CP-60,300 (the marker residue for tulathromycin) residues.

Results: Results are summarized in the tables below.

Table IV.E.1.c (1) 1. Concentrations of CP-60,300 (mean ± standard deviation; in ppm) in cattle tissues following treatment of a single subcutaneous injection containing 3 mg ketoprofen/kg bw and 2.5 mg tulathromycin/kg bw.

Withdrawal Period (days)	Kidney	Liver	Muscle	Fat
1	4.41 ±0.72	2.91 ± 0.58	1.13 ± 0.24	0.388 ± 0.072
4	5.53 ± 0.63	3.94 ± 1.39	0.892 ± 0.27	0.223 ± 0.037
7	4.24 ± 0.31	4.06 ± 0.49	0.408 ± 0.066	0.136 ± 0.014
12	3.26 ± 0.7	3.37 ± 0.41	0.308 ± 0.13	0.168 ± 0.054
18	1.77 ± 0.038	2.73 ± 0.44	0.113 ± 0.010	0.0655 ± 0.010
24	1.04 ± 0.32	1.89 ± 0.37	0.0719 ± 0.019	< LOQ
30	0.554 ± 0.12	1.80 ± 0.27	0.0742*	< LOQ
36	0.350 ± 0.25	0.955 ±0.16	0.0676*	< LOQ

LOQ: Limit of Quantitation, 0.05 ppm
*Only one value above LOQ

Table IV.E.1.c (1) 2. Concentrations of CP-60,300 (mean ± standard deviation; in ppm) in cattle injection site following treatment of a single subcutaneous injection containing 3 mg ketoprofen/kg bw and 2.5 mg tulathromycin/kg bw.

Withdrawal Period (days)	Core Injection Site	Ring Injection Site
1	108.9 ± 73.3	3.375 ± 1.70
4	11.18 ± 23.0	5.015 ± 2.71
7	10.36 ± 26.1	2.938 ± 1.50
12	7.130 ± 12.6	2.725 ± 1.63
18	7.823 ± 0.484	2.555 ± 1.78
24	4.920 ± 2.02	2.145 ± 0.996
30	5.490 ± 0.946	1.987 ± 2.65
36	2.845 ± 0.646	1.163 ± 1.04

Table IV.E.1.c (1) 3. Concentrations of ketoprofen (mean ± standard deviation; in ppm) in cattle tissues following treatment of a single subcutaneous injection containing 3 mg ketoprofen/kg bw and 2.5 mg tulathromycin/kg bw.

Withdrawal Period (days)	Kidney	Liver	Muscle	Fat
1	1.21 ± 1.1	0.0155*	0.0223 ± 0.0098	0.0311 ± 0.017
4	< LOQ	< LOQ	< LOQ	0.0153*
7	< LOQ	0.0513*	< LOQ	< LOQ
12	< LOQ	< LOQ	< LOQ	0.0118*

LOQ: Limit of Quantitation, 0.01 ppm
*only one value above LOQ

Table IV.E.1.c (1) 4. Concentrations of ketoprofen (mean ± standard deviation; in ppm) in cattle injection site following treatment of a single subcutaneous injection containing 3 mg ketoprofen/kg bw and 2.5 mg tulathromycin/kg bw.

Withdrawal Period (days)	Core Injection Site	Ring Injection Site
1	115.7 ± 117	0.566 ± 0.27
4	200*	0.0116 ± 0.0013
7	0.0416 ± 0.025	< LOQ
12	0.007**	< LOQ

LOQ: Limit of Quantitation, 0.01 ppm
*only two values above LOQ
**only one value above LOQ

Concentrations of CP-60,300 persist longer above its tolerance than concentrations of ketoprofen. Therefore, depletion of CP-60,300 was used to calculate a withdrawal period. Tissue residue data were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99th percentile of the population with 95% confidence. The data support assignment of an 18-day withdrawal period. A withdrawal period of 18 days is consistent with depletion of residues at the injection site.

2. Target Tissue and Marker Residue

Tulathromycin

The target tissue is liver, and the marker residue is CP-60,300 (21 CFR 556.745).

Ketoprofen

The target tissue is kidney and the marker residue is ketoprofen (21 CFR 556.345).

3. Tolerances

   Tulathromycin

   A tolerance of 5.5 ppm for CP-60,300 in cattle liver was established previously (21 CFR 556.745).

   Ketoprofen

   A tolerance of 0.36 ppm for ketoprofen in cattle kidney was established previously (21 CFR 556.345).

4. Withdrawal Period

   Tissue residue data from Study No. A433N-US-18-615 were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99th percentile of the population with 95% confidence. The data support assignment of an 18-day withdrawal period for Draxxin® KP when used according to label directions in cattle. A withdrawal period of 18 days is consistent with depletion of residues at the injection site.

D. Analytical Method for Residues

1. Description of Analytical Method

   Tulathromycin

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

   Ketoprofen

   The FOI Summary for the supplemental approval of NADA 140-269, dated May 25, 2021, contains the analytical method summary for ketoprofen in cattle.

2. Availability of the Method

   The validated analytical methods for analysis of residues of tulathromycin and ketoprofen are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Draxxin® KP:

"USER SAFETY WARNINGS: Not for human use. Keep out of reach of children. The Safety Data Sheet (SDS) provides more detailed occupational safety information. To obtain a Safety Data Sheet contact Zoetis Inc. at 1-888-963-8471."

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Draxxin® KP, when used according to the label, is safe and effective for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, and control of pyrexia associated with BRD in beef steers, beef heifers, beef calves 2 months of age and older, beef bulls, dairy bulls, and replacement dairy heifers. Additionally, data demonstrate that residues in food products derived from species treated with Draxxin® KP 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 order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, professional expertise is required to monitor the safe use of this product, and restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product in animals in order to mitigate the potential for development of bacterial resistance to antimicrobial drugs.

B. Exclusivity

Draxxin® KP, as approved, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Draxxin® KP.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.