Date of Approval: December 28, 2007

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-244

DRAXXIN Injectable Solution

Tulathromycin
Beef and non-lactating dairy cattle
and swine

1. For the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*
2. To add *Mycoplasma hyopneumoniae* to the list of pathogens for the swine respiratory disease indication

Sponsored by:

Pfizer, Inc.

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## I. GENERAL INFORMATION:

| | |
|---|---|
| **A. File Number:** | NADA 141-244 |
| **B. Sponsor:** | Pfizer, Inc.<br>235 East 42d St.<br>New York, NY 10017<br><br>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):** | Cattle: DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*), and *Mycoplasma bovis;* and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*. **DRAXXIN Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.**<br><br>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 1) the addition of a new indication, for the treatment of IBK associated with *Moraxella bovis* in cattle, and 2) the addition of *Mycoplasma hyopneumoniae* to the list of pathogens for the SRD indication.

## II. EFFECTIVENESS:

### A. Dosage Characterization:

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

### B. Substantial Evidence:

**Addition of an IBK Indication in Cattle:**

#### 1. Field Study

a. Title: Efficacy of Tulathromycin Injectable Solution for the Treatment of Infectious Bovine Keratoconjunctivitis Associated with *Moraxella bovis*. Study Report No. 1133C-60-04-434. September 2004 to October 2004.

b. Study Investigator and Location: Terry TerHune, D.V.M., Ph.D., HMS Veterinary Development, Inc., Reedley, California.

c. Study Design:

*1) Objective:* To evaluate the effectiveness of DRAXXIN (tulathromycin) Injectable Solution administered subcutaneously (SC) once at a dose of 2.5 mg/kg body weight (BW) for the treatment of IBK associated with *Moraxella bovis*.

*2) Test Animals:* One hundred male mixed breed beef calves, between 4 and 10 months of age, weighing 138 to 342 kg were enrolled.

*3) Experimental Design:* Calves were enrolled in the study when they had at least one clinical sign of IBK and the presence of an ulcer in one or both eyes. Eligible calves were grouped by corneal damage score, ranked by

the number of clinical signs present, and then assigned to blocks of two animals each. Calves within a block were randomly assigned to saline or tulathromycin treatment groups in a 1:1 ratio. Within a pen, all calves were enrolled on the same day.

4) *Treatment Groups:*

Table 1. Treatment Groups, Study Report No. 1133C-60-04-434

| Treatment | Dosage | Number of Animals |
|---|---|---|
| saline | 0.025 mL/kg BW* SC once | 50 |
| tulathromycin | 2.5 mg/kg BW SC once | 50 |

*volume equivalent to tulathromycin dosage

5) *Test Article Administration:* The test article was tulathromycin sterile injectable solution. The control article was commercial physiological saline (0.9% sodium chloride) sterile injectable solution. Treatments were administered subcutaneously in the left side of the neck once on the day of enrollment.

6) *Measurements and Observations:* Clinical signs of IBK were recorded at enrollment (Day 0) and then every other day beginning on Day 3 (Days 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21). The presence or absence of an ulcer was assessed by fluorescein staining on Day 0 and then on Days 5, 9, 13, 17, and 21. Both eyes of every enrolled calf were examined at each time point.

7) *Statistical Analysis:* The individual calf was the experimental unit. The primary variable for effectiveness was cure rate, which was assessed at Days 5, 9, 13, 17, and 21 post-treatment. A calf was considered cured if the affected eye(s) was normal and the calf had not been removed from the study for non-IBK reasons. The cure rates of the tulathromycin-treated and control groups were compared at each assessment day using the Cochran-Mantel-Haenszel test.

Time to improvement was evaluated as a secondary variable. Time to improvement was defined as the first day on which a calf had no clinical signs of IBK for both eyes, provided that there were also no clinical signs of IBK for both eyes on the next day of observation. Time to improvement was analyzed using the log-rank test to compare the survival curves of the tulathromycin-treated and control groups.
All tests were done at the 0.05 significance level.

d. Results: Ninety-eight calves (49 control, 49 tulathromycin) completed the study. One saline-treated calf was dropped from the analysis because it

developed acute bovine respiratory disease on Day 2 and was euthanized. One tulathromycin-treated calf died on Day 7 from acute rumen bloat.

*1) Cure Rate:*

Table 2. Cure Rates, Study Report No. 1133C-60-04-434

| Study Day | Number of Cures | | P-value |
|---|---|---|---|
| | Tulathromycin | Saline | |
| Day 5 | 24/50 (48.0%) | 1/49 (2.0%) | P < 0.0001 |
| Day 9 | 49/49 (100%) | 4/49 (8.2%) | P < 0.0001 |
| Day 13 | 49/49 (100%) | 12/49 (24.5%) | P < 0.0001 |
| Day 17 | 49/49 (100%) | 41/49 (83.7%) | P = 0.0033 |
| Day 21 | 49/49 (100%) | 43/49 (87.8%) | P = 0.0119 |

*2) Time to Improvement:* The tulathromycin-treated group had a significantly lower time to improvement curve than the saline-treated group (P < 0.0001). The mean times to improvement for the tulathromycin-treated and saline-treated groups were 6.2 days and 15.1 days, respectively.

e. Adverse Reactions: No test article-related adverse reactions were reported.

f. Conclusion: DRAXXIN (tulathromycin) Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, was effective for the treatment of IBK associated with *Moraxella bovis* in cattle.

**2. Field Study**

a. Title: Efficacy of Tulathromycin Injectable Solution for the Treatment of Infectious Bovine Keratoconjunctivitis Associated with *Moraxella bovis*. Study Report No. 1133C-60-04-435. July 2004 to August 2004.

b. Study Investigator and Location: Larry L. Smith, DVM, Larry Smith Farms, Readstown, Wisconsin.

c. Study Design:

*1) Objective:* To evaluate the effectiveness of DRAXXIN (tulathromycin) Injectable Solution administered subcutaneously (SC) once at a dose of 2.5 mg/kg body weight (BW) for the treatment of IBK associated with *Moraxella bovis*.

*2) Test Animals:* One hundred castrated male beef crossbred, castrated male Holstein, and female beef crossbred calves, between 6 and 14 months of age, weighing 156 to 395 kg were enrolled.

3) *Experimental Design:* Calves were enrolled in the study when they had at least one clinical sign of IBK and the presence of an ulcer in one or both eyes. Eligible calves were grouped by corneal damage score, ranked by the number of clinical signs present, and then assigned to blocks of two animals each. Calves within a block were randomly assigned to saline or tulathromycin treatment groups in a 1:1 ratio. Calves were maintained in three separate pastures, based on owner and date of enrollment. Each pasture contained blocks of animals with different enrollment dates.

4) *Treatment Groups:*

Table 3. Treatment Groups, Study Report No. 1133C-60-04-435

| Treatment | Dosage | Number of Animals |
|---|---|---|
| saline | 0.025 mL/kg BW* SC once | 50 |
| tulathromycin | 2.5 mg/kg BW SC once | 50 |

*volume equivalent to tulathromycin dosage

5) *Test Article Administration:* The test article was tulathromycin sterile injectable solution. The control article was commercial physiological saline (0.9% sodium chloride) sterile injectable solution. Treatments were administered subcutaneously in the left side of the neck once on the day of enrollment.

6) *Measurements and Observations:* Clinical signs of IBK were recorded at enrollment (Day 0) and then every other day beginning on Day 3 (Days 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21). The presence or absence of an ulcer was assessed by fluorescein staining on Day 0 and then on Days 5, 9, 13, 17, and 21. Both eyes of every enrolled calf were examined at each time point.

7) *Statistical Analysis:* The individual calf was the experimental unit. The primary variable for effectiveness was cure rate, which was assessed at Days 5, 9, 13, 17, and 21 post-treatment. A calf was considered cured if the affected eye(s) was normal and the calf had not been removed from the study for non-IBK reasons. Cure rate was analyzed using a generalized linear mixed model with repeated measures, and pair wise comparisons were done to test for a treatment effect on each assessment day. Pasture, treatment by pasture, and block within pasture were included as random effects.

Time to improvement was evaluated as a secondary variable. Time to improvement was defined as the first day on which a calf had no clinical signs of IBK for both eyes, provided that there were also no clinical signs of IBK for both eyes on the next day of observation. Time to

improvement was analyzed using the log-rank test to compare the survival curves of the tulathromycin-treated and control groups.

All tests were done at the 0.05 significance level.

d. Results: Eighty-three calves (37 control, 46 tulathromycin) completed the study. Sixteen calves (12 saline-treated calves and 4 tulathromycin-treated calves) were removed from the study due to perforating corneal ulcers. These animals were counted as failures in the cure rate and time to improvement analyses for all days after removal. One saline-treated calf was removed from the data analysis because the enrollment criteria could not be verified.

*1) Cure Rate:*

Table 4. Cure Rates, Study Report No. 1133C-60-04-435

| Study Day | Number of Cures* | | P-value |
|---|---|---|---|
| | Tulathromycin | Saline | |
| Day 5 | 15/50 (24.9%) | 4/49 (4.7%) | P = 0.0004 |
| Day 9 | 25/50 (49.4%) | 11/49 (16.6%) | P = 0.0005 |
| Day 13 | 34/50 (72.3%) | 10/49 (13.7%) | P < 0.0001 |
| Day 17 | 39/50 (83.8%) | 19/49 (35%) | P < 0.0001 |
| Day 21 | 40/50 (85%) | 18/49 (32.2%) | P < 0.0001 |

*The percents listed are the back-transformed least-squares means from the analysis on cure rate. They are not equal to the raw percents.

*2) Time to Improvement:* The tulathromycin-treated group had a significantly lower time to improvement curve than the saline-treated group (P < 0.0001). The mean times to improvement for the tulathromycin-treated and saline-treated groups were 10.7 days and 14.6 days, respectively.

e. Adverse Reactions: No test article-related adverse reactions were reported.

f. Conclusion: DRAXXIN (tulathromycin) Injectable Solution, administered as a single SC dose of 2.5 mg/kg BW, was effective for the treatment of IBK associated with *Moraxella bovis* in cattle.

**3. Determination of Minimum Inhibitory Concentrations (MICs)**

The MICs of tulathromycin were determined for *Moraxella bovis* isolates obtained from calves enrolled in the IBK studies described above. Isolates were obtained from pre-treatment conjunctival swabs from all calves enrolled in the study. MICs were determined using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). The results are shown in the following table.

Table 5. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating IBK in the U.S.

| Indicated pathogen | Date isolated | No. of isolates | $MIC_{50}$ ** (µg/mL) | $MIC_{90}$ ** (µg/mL) | MIC range (µg/mL) |
|---|---|---|---|---|---|
| *Moraxella bovis* | 2004 | 55 | 0.5 | 0.5 | 0.25 to 1 |

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

**Addition of *M. hyopneumoniae* to the SRD Indication in Swine:**

Effectiveness of tulathromycin 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, and is summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244) dated May 24, 2005.

Effectiveness of tulathromycin for the treatment of SRD associated with *Mycoplasma hyopneumoniae* was demonstrated by two experimentally-induced infection model studies and the *M. hyopneumoniae* data from SRD studies for the original approval of DRAXXIN Injectable Solution.

**1. Induced Infection Model Study**

a. Title: Efficacy of Tulathromycin for the Treatment of Experimentally-Induced *Mycoplasma hyopneumoniae* Infection in Swine. Study No. 1121C-60-03-209. January 2006 to March 2006.

b. Study Investigator and Location: Kelly Lechtenberg, DVM, PhD, Midwest Veterinary Services, Inc., Oakland, Nebraska.

c. Study Design:

*1) Objective:* To investigate the effectiveness of tulathromycin injectable solution administered as a single, intramuscular (IM) dose of 2.5 mg/kg body weight (BW) in the treatment of experimentally-induced *M. hyopneumoniae* pneumonia in swine.

*2) Test Animals:* Ninety-two commercial crossbred female and castrated male pigs were enrolled. Pigs were approximately 8.5 weeks of age and weighed between 18.6 and 38.1 kg. Only pigs that were healthy and serologically negative for *M. hyopneumoniae* on arrival were included in the study.

*3) Experimental Design:* Pigs were challenged on three consecutive days by endotracheal and intranasal inoculation of a lung homogenate containing

$10^5$ *M. hyopneumoniae* per mL. The isolate used was obtained from a pig with typical *M. hyopneumoniae* lung lesions in Missouri in 2004.

Nine days post-infection, eligible pigs were randomly assigned to one of twelve study pens and one of three treatments (T01, T02, or NTX). Treatment groups were commingled in pens. NTX pigs were euthanized at specified intervals throughout the study and necropsied to establish Day 0 (day of treatment) and monitor disease progression. Day 0 was defined as the day that at least 4 of the 5 NTX pigs euthanized that day had weighted gross pneumonic lung lesions of at least 5%. In this study, Day 0 occurred 10 days after the first day of infection. On Day 10, all remaining pigs in the T01 and T02 groups were weighed and euthanized, and postmortem examination was performed.

4) *Treatment Groups:*

Table 6. Treatment Groups, Study No. 1121C-60-03-209

| Group | Treatment | Dosage | No. of Animals |
|---|---|---|---|
| T01 | saline | 0.025 mL/kg BW* IM once | 36 (3 per pen) |
| T02 | tulathromycin | 2.5 mg/kg BW IM once | 36 (3 per pen) |
| NTX | no treatment | --- | 20 (1-2 per pen) |

*volume equivalent to tulathromycin dosage

5) *Test Article Administration:* The test article was tulathromycin sterile injectable solution. The control article was commercial physiological saline (0.9% sodium chloride) sterile injectable solution. Treatments were administered to the T01 and T02 groups by IM injection in the neck once on Day 0.

6) *Measurements and Observations:* Pigs were weighed on Day 0 and Day 10. General health observations were performed twice daily from arrival until the end of the study. From Day 3 to Day 10, pigs were clinically evaluated and scored once daily for cough, respiration, and attitude.

Postmortem examination was performed on all T01, T02, and NTX pigs, including those that died or were euthanized during the study. For each pig, the percent of gross pneumonic lung involvement was determined for each lobe and weighted 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%. The lung lesion score (percentage of total lung with lesions) for each pig was calculated by summing the weighted lung lobe values across lobes.

Lung lavage fluid and pneumonic lung tissue samples were collected from each pig for bacterial isolation and identification.

7) *Statistical Analysis:* The pig was the experimental unit. The primary variable was lung lesion score. Clinical scores (attitude, respiration, and cough) and average daily weight gain (Day 0 to 10) were analyzed as secondary variables.

Lung lesion score and average daily gain were analyzed using a linear mixed model, with fixed effect treatment and random effect pen. The 5% level of significance ($p \leq 0.05$) was used to assess statistical differences. The arcsine square root transformation was applied to the lung lesion scores prior to analysis, and the mean lung lesion score per group was estimated by back-transforming the least squares mean estimate from the analysis. Clinical scores were summarized by treatment group.

d. Results: Thirty-six saline-treated pigs and 35 tulathromycin-treated pigs were included in the analyses (except lung lesion scores, where 36 saline-treated pigs and 34 tulathromycin-treated pigs were included). One tulathromycin-treated pig was removed and euthanized due to lameness. An additional tulathromycin-treated pig was removed from the lung lesion score analysis due to incomplete data collection.

1) *Lung Lesion Scores:* The weighted percentage of total lung lesions in the tulathromycin-treated group (8.52%) was statistically significantly lower ($p < 0.0001$) than in the saline-treated group (23.62%).

2) *Clinical Scores:* On all study days when there were pigs with abnormal respiratory and cough scores, fewer tulathromycin-treated pigs had abnormal scores than saline-treated pigs. In addition, the tulathromycin-treated group had fewer days with pigs with abnormal attitude scores than saline-treated group.

3) *Average Daily Gain:* Tulathromycin-treated pigs had a higher average daily gain compared to the saline-treated pigs.

e. Adverse Reactions: No test article-related adverse reactions were reported.

f. Conclusion: DRAXXIN (tulathromycin) Injectable Solution, administered as a single IM dose of 2.5 mg/kg BW, decreased lung lesions in treated animals with experimentally-induced SRD associated with *M. hyopneumoniae*.

**2. Induced Infection Model Study**

a. Title: Efficacy of Tulathromycin for the Treatment of Experimentally-Induced *Mycoplasma hyopneumoniae* Infection in Swine. Study No. 1121C-60-04-230. January 2006 to March 2006.

b. Study Investigator and Location: Lyle Kesl, DVM, PhD, Veterinary Resources, Inc., Ames, Iowa.

c. Study Design:

*1) Objective:* To investigate the effectiveness of tulathromycin injectable solution administered as a single IM dose of 2.5 mg/kg BW in the treatment of experimentally-induced *M. hyopneumoniae* pneumonia in swine.

*2) Test Animals:* Ninety-two commercial crossbred female and castrated male pigs were enrolled. Pigs were approximately 9 weeks of age and weighed between 21.2 and 51.8 kg. Only pigs that were healthy and serologically negative for *M. hyopneumoniae* on arrival were included in the study.

*3) Experimental Design:* Pigs were challenged on three consecutive days by endotracheal and intranasal inoculation of a lung homogenate containing $10^5$ *M. hyopneumoniae* per mL. The isolate used was obtained from a pig with typical *M. hyopneumoniae* lung lesions in Missouri in 2004.

Nine days post-infection, eligible pigs were randomly assigned to one of twelve study pens and treatments (T01, T02, or NTX). Treatment groups were commingled in pens. NTX pigs were euthanized at specified intervals throughout the study and necropsied to establish Day 0 (day of treatment) and monitor disease progression. Day 0 was defined as the day that at least 4 of the 5 NTX pigs euthanized that day had weighted gross pneumonic lung lesions of at least 5%. In this study, Day 0 occurred 10 days after the first day of infection. On Day 10, all remaining pigs in the T01 and T02 groups were weighed and euthanized, and postmortem examination was performed.

*4) Treatment Groups:*

Table 7. Treatment Groups, Study No. 1121C-60-04-230

| Group | Treatment | Dosage | No. of Animals |
|---|---|---|---|
| T01 | saline | 0.025 mL/kg BW* IM once | 36 (3 per pen) |
| T02 | tulathromycin | 2.5 mg/kg BW IM once | 36 (3 per pen) |
| NTX | no treatment | --- | 20 (1-2 per pen) |

*volume equivalent to tulathromycin dosage

*5) Test Article Administration:* The test article was tulathromycin sterile injectable solution. The control article was commercial physiological saline (0.9% sodium chloride) sterile injectable solution. Treatments were administered to the T01 and T02 groups by IM injection in the neck once on Day 0.

6) *Measurements and Observations:* Pigs were weighed on Day 0 and Day 10. General health observations were performed twice daily from arrival until the end of the study. From Day 3 to Day 10, pigs were clinically evaluated and scored once daily for cough, respiration, and attitude.

   Postmortem examination was performed on all T01, T02, and NTX pigs, including those that died or were euthanized during the study. For each pig, the percent of gross pneumonic lung involvement was determined for each lobe and weighted 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%. The lung lesion score (percentage of total lung with lesions) for each pig was calculated by summing the weighted lung lobe values across lobes.

   Lung lavage fluid and pneumonic lung tissue samples were collected from each pig for bacterial isolation and identification.

7) *Statistical Analysis:* The pig was the experimental unit. The primary variable was lung lesion score. Clinical scores (attitude, respiration, and cough) and average daily weight gain (Day 0 to 10) were analyzed as secondary variables.

   Lung lesion scores and average daily gain were analyzed using a linear mixed model, with fixed effect treatment and random effect pen. The 5% level of significance ($p \leq 0.05$) was used to assess statistical differences. The arcsine square root transformation was applied to the lung lesion scores prior to analysis, and the mean lung lesion score per group was estimated by back-transforming the least squares mean estimate from the analysis. Clinical scores were summarized by treatment group.

d. Results: Thirty-five saline-treated pigs and 36 tulathromycin-treated pigs were included in the analyses (except for average daily gain, where 34 saline-treated pigs and 36 tulathromycin-treated pigs were included). One saline-treated pig died during the study and was diagnosed with a gastric ulcer. One additional saline-treated pig was excluded from the average daily gain analysis because its Day 10 body weight was inadvertently not recorded.

   1) *Lung Lesion Scores:* The weighted percentage of total lung lesions in the tulathromycin-treated group (11.31%) was statistically significantly lower ($p < 0.0001$) than the saline-treated group (26.42%).

   2) *Clinical Scores:* The tulathromycin-treated pigs had no days with pigs with abnormal attitude or respiration scores, compared to 7 days for the saline-treated pigs. There were fewer tulathromycin-treated pigs with

abnormal coughing scores on days when both groups had pigs with abnormal scores compared to the saline-treated pigs.

3) *Average Daily Gain:* Tulathromycin-treated pigs had a higher average daily gain compared to the saline-treated pigs.

e. Adverse Reactions: No test article-related adverse reactions were reported.

f. Conclusion: DRAXXIN (tulathromycin) Injectable Solution, administered as a single IM dose of 2.5 mg/kg BW, decreased lung lesions in treated animals with experimentally-induced SRD associated with *M. hyopneumoniae*.

**3. Field Studies**

Data from the SRD field studies summarized in the FOI Summary for DRAXXIN Injectable Solution (NADA 141-244) dated May 24, 2005, were examined. The cure rate (combined across all study sites) was statistically significantly higher ($p = 0.0214$) for the tulathromycin-treated pigs (189/266, 70.54%) than for the saline-treated pigs (124/267, 46.09%). *M. hyopneumoniae* isolates were obtained from 106 saline-treated and non-treated sentinel pigs at five of the six study sites (Study 1123C-60-01-193, 1123C-60-01-195, 1123C-60-01-196, 1123C-60-01-198, and 1123C-02-01-192). The data demonstrate that tulathromycin had a therapeutic effect under field use conditions where *M. hyopneumoniae* was present.

## 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 and 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 cattle and swine.

### C. Microbial Food Safety:

The impact of the proposed change to approved tulathromycin (as DRAXXIN Injectable Solution) to include a new indication in cattle - for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis* - on microbial food safety was carefully considered by the Agency. The Agency determined that this change should not significantly impact public health, and therefore an evaluation of microbial food safety regarding this change was not necessary at this time.

The impact of the proposed change in indication for approved tulathromycin (as DRAXXIN Injectable Solution) to include a new pathogen - for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica, Haemophilus parasuis,* **and *Mycoplasma hyopneumoniae*** - in swine was carefully considered by the Agency. The Agency determined that the addition of this new pathogen to the previously approved indication should not significantly impact public health, and therefore an evaluation of microbial food safety regarding this change was not necessary at this time.

### D. Analytical Method for Residues:

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

## 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 IBK associated with *Moraxella bovis* and for the treatment of SRD associated with *Mycoplasma hyopneumoniae*. Additionally, data demonstrate that residues in food products derived from cattle and 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 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 IBK and SRD, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

**B. Exclusivity:**

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the IBK indication and the treatment of SRD associated with *M. hyopneumoniae* for which this supplement is approved.

**C. Supplemental Applications:**

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

**D. Patent Information:**

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

| U.S. Patent Number | Date of Expiration |
|---|---|
| 6,329,345 | November 18, 2019 |
| 6,420,536 | May 29, 2018 |
| 6,514,945 | January 24, 2021 |
| 6,583,274 | May 2, 2020 |
| 6,777,393 | May 29, 2018 |

## VII. ATTACHMENTS:

Facsimile Labeling:

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