Date of Approval: November 30, 2017

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 097-505

LINCOMIX® 20
LINCOMIX® 50

lincomycin

Type A medicated article

Swine

For reduction in the severity of the effects of respiratory disease associated with *Mycoplasma hyopneumoniae*.

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 097-505

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

LINCOMIX® 20 and LINCOMIX® 50

D. Product Established Name

Lincomycin

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Type A medicated article

G. Amount of Active Ingredient

20 g lincomycin/lb and 50 g lincomycin/lb, respectively

H. How Supplied

50 lb bags (22.7 kg)

I. Dispensing Status

VFD

J. Dosage Regimen

100 to 200 g lincomycin/ton of complete feed as the sole ration for 21 days

K. Route of Administration

Oral in feed

L. Species/Class

Swine

M. Indication

For reduction in the severity of the effects of respiratory disease associated with *Mycoplasma hyopneumoniae*.

N. Effect of Supplement

This supplement modernizes the language of the previously approved indication "for reduction in the severity of swine mycoplasmal pneumonia caused by *Mycoplasma hyopneumoniae*" to read "for reduction in the severity of the effects of respiratory disease associated with *Mycoplasma hyopneumoniae*"; and adds a range of approved feed inclusion rates to provide for the use of lincomycin at 100 to 200 grams per ton of complete feed, fed as the sole ration for 21 consecutive days, for reduction in the severity of the effects of respiratory disease associated with *Mycoplasma hyopneumoniae.*

II. EFFECTIVENESS

A. Dosage Characterization

LINCOMIX® 20 and LINCOMIX® 50 Type A medicated articles have been approved for use in swine at an inclusion rate of 200 grams lincomycin per ton of complete feed for reduction in the severity of swine mycoplasmal pneumonia caused by *Mycoplasma hyopneumoniae* when administered for 21 days. See the FOI Summary for NADA 097-505 dated November 19, 1982, which contains a summary of a dose range-finding, induced infection challenge model study (Trial No. 524-9660-2-MJD-75-17). This study included a 100 grams lincomycin per ton treatment group that demonstrated a reduction in incidence and severity of gross lung lesions when compared with the control group.

B. Substantial Evidence

1. Natural Infection Field Study

   Title: "A dose confirmation study evaluating 100 g/ton of LINCOMIX® (lincomycin hydrochloride) for the reduction of the severity of effects of respiratory disease associated with *Mycoplasma hyopneumoniae*". (Study No. A121C-US-14-150).

   Study Dates: October 2014 to March 2017.

   Study Locations:

   Fairfax, Minnesota
   Oakman, Alabama
   Oakland, Nebraska
   Story City, Iowa
   Williams, Iowa
   Dalhart, Texas
   Manhattan, Kansas

Study Design:

Objective: To evaluate the effectiveness of 100 grams lincomycin per ton of complete feed administered to swine for 21 days for reduction in the severity of the effects of respiratory disease associated with *M. hyopneumoniae*. The study was conducted in accordance with Guidance for Industry (GFI) #85 "Good Clinical Practice (GCP)" (VICH GL9).

Study Animals: A total of 1720 commercial crossbred male and female pigs, weighing between 15 kg and 114.8 kg were enrolled across 8 sites. Within a study site, pigs were in the same production class (either grower or finisher). Source herds were selected based on a history of or risk factors associated with *M. hyopneumoniae*. When at least 20% of a minimum of 100 pigs in the source herd were polymerase chain reaction (PCR) positive for *M. hyopneumoniae,* the source herd was eligible for enrollment and transported to the study site as necessary.

Experimental Design: The study was a randomized, masked, multi-site, natural infection field study. Upon qualification for enrollment, pigs were placed in pens for the pre-treatment period, which ranged from 0 to 6 days. Pigs were excluded from enrollment if they exhibited signs of acute swine respiratory disease (SRD). Acute SRD was defined as a respiratory score of ≥2 (on a scale from 0 [normal] to 3 [severe]) and depression score of ≥2 (on a scale from 0 [normal] to 3 [severe]) and rectal temperature ≥104°F. Pigs were also excluded from enrollment if their respiratory score or depression score was 3, or if they exhibited other signs of abnormal health. On Day 0 (enrollment and treatment initiation), pigs were weighed and allocated to pens and treatments according to a randomized complete block design at each site. Body weight was a blocking factor. Animals within the same pen were assigned to the same treatment. A block consisted of one lincomycin-treated pen and one non-treated, negative control pen. The experimental unit for the study was the pen. At each site, there were 10 to 12 pigs per pen, and 100 to 120 pigs per treatment group. A total of 860 pigs were enrolled in each treatment group across the study. One control-group pig was excluded from the analysis due to the inability to confirm pre-enrollment criteria.

From Days 1 to 21, if a pig met the criteria for acute SRD, had a respiratory score or a depression score of 3, or had other signs of abnormal health, the pig was removed from the study and subject to necropsy and lung lesion evaluation. Based on the study definition of acute SRD, all pigs were evaluated and classified as "with acute SRD" or "without acute SRD" on Day 21, or upon death or removal before Day 21. Pigs that were removed for a respiratory score or a depression score of 3, were classified as "with acute SRD" unless another cause was diagnosed. At the end of the study (Day 21 or 22 depending on workload at the site), all remaining pigs were euthanized for necropsy and lung lesion evaluation. The individuals performing clinical assessments and necropsies were masked to treatment and did not participate in treatment administration.

Drug Administration: The test article was LINCOMIX® 50 Type A medicated article administered at 100 grams lincomycin per ton of complete swine feed (Type C medicated feed). Non-medicated complete swine feed was used as the control article. Treatment began on Day 0 and pigs were administered the test article or the control article as the sole ration *ad libitum* for 21 consecutive days (through Day 21).

Measurements and Observations: Once daily general health observations were recorded during the pre-treatment period and continued through the end of the study. Body weights were recorded on Day 0 and Day 21 (or Day 22 depending on workload at the site), and upon death or removal from the study prior to end of study.

During the pre-treatment period, pigs were observed for signs of acute SRD. Immediately prior to enrollment on Day 0, all pigs had respiratory and depression scores recorded. If the respiratory score was ≥2 or the depression score was ≥2, the rectal temperature was also recorded. From Day 1 to Day 21, pigs had respiratory and depression scores recorded for any pig with respiratory score ≥2 or depression score ≥2. Rectal temperature was also recorded: for any pig that had a respiratory score =2 and depression score =2; and for any pig that had a respiratory score =3 or depression score =3. Physical examinations were conducted by the study veterinarian as needed.

All pigs were necropsied on Day 21 (or Day 22 depending on workload at the site) or upon death/removal from the study. At necropsy, the percentage of pneumonic lung lesions was estimated and a weighted lung lesion score was determined using the following ratios of individual lung lobes to total lung mass: left cranial 10%, left middle 10%, left caudal 25%, right cranial 10%, right middle 10%, right caudal 25%, and accessory 10%. Lung homogenates of samples collected at necropsy from the control group pigs on Day 21, and from all pigs that either died or were euthanized prior to Day 21 or that met the criteria for acute SRD on any day, were analyzed using a quantitative PCR method to prioritize samples for culture to recover isolates of *M. hyopneumoniae*. Recovered isolates were confirmed as *M. hyopneumoniae* by PCR.

Statistical Methods:

The primary variable was the percentage of pneumonic lung lesions. The arcsine square root transformation was applied to the percentage of total lung lesions prior to analysis. Then the transformed percentage was analyzed using a linear mixed model. The model included treatment as the fixed effect and site, the site-by-treatment interaction, block within site, and the block-by-treatment interaction within site (pen) as the random effects.

Average daily gain (ADG) was analyzed using a linear mixed model. The model included treatment as the fixed effect and site, the site-by-treatment interaction, block within site, and the block-by-treatment interaction within site (pen) as the random effects. Day 0 body weight was used as a covariate in the model.

Results:

Primary Variable: The percentage of total lung with lesions was significantly different (P=0.001), and numerically less in the lincomycin-treated group compared to the control group. The back transformed least squares means (LSM) for the lincomycin-treated group and the control group were 15.2% and 20.3%, respectively. One pig from the lincomycin-treated group was excluded from the lung lesion analysis due to inability to score the lung lesions.

Clinical Relevance of Lung Lesions: Across all sites, the incidence of acute SRD in the lincomycin-treated group (27/860) was numerically lower than the incidence of acute SRD in the control group (35/859). The observed incidence of acute SRD and relevant observations from the pen ADG results across all sites validated that the observed lung lesion results are clinically relevant.

Presence and Involvement of M. hyopneumoniae: A total of 57 isolates of *M. hyopneumoniae* were cultured from 109 pigs. In addition, 756 of 892 (85%) of lung samples collected at necropsy were verified as being positive for *M. hyopneumoniae* by PCR.

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

Conclusions:

This study demonstrates that lincomycin is effective for reduction in the severity of the effects of respiratory disease associated with *Mycoplasma pneumoniae* when administered to swine at 100 grams lincomycin per ton of complete feed as the sole ration for 21 days.

2. Therapeutic Effect Against *M. hyopneumoniae*

Studies conducted for the original approval of the *M. hyopneumoniae* indication (Trial No. 524-9660-2-MJD-75-17, an induced infection model study, and Trial Nos. 524-9660-2-MJD-76-33, -76-38, -77-01, -77-03, a natural infection field study) support that lincomycin has a therapeutic effect against *M. hyopneumoniae* when administered to swine at 100 grams lincomycin per ton of complete feed as the sole ration for 21 days. The FOI Summary for NADA 097-505 dated November 19, 1982, contains a summary of these studies.

Study No. A121C-US-14-150 also supports that lincomycin has a therapeutic effect against *M. hyopneumoniae* when administered to swine at 100 grams lincomycin per ton of complete feed as the sole ration for 21 days.

Together, these studies demonstrate that lincomycin has a therapeutic effect against *M. hyopneumoniae* when administered to swine at 100 grams lincomycin per ton of complete feed as the sole ration for 21 days.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the supplemental approval of NADA 097-505 dated November 19, 1982, contains a summary of target animal safety studies for swine.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

Microbial food safety (antimicrobial resistance) information for lincomycin was evaluated using an updated hazard characterization and qualitative risk assessment to address FDA's concern for the development of antimicrobial resistant *Campylobacter* spp. in or on food derived from lincomycin-treated swine.

The evaluation of this information and additional consideration of the proposed therapeutic use in groups of swine and not entire herds, have resulted in CVM's individual rankings of *low* for the release assessment, *medium* for the exposure assessment, and *highly important* for the consequence assessment. It was determined that the overall risk estimation associated with the use of lincomycin in swine under the proposed conditions is *medium* and corresponds with mitigation strategies assigned to Category 2 antimicrobial drugs for food-animal use. Risk management steps for a Category 2 antimicrobial drug include Veterinary Feed Directive (VFD) marketing status, extra-label use restriction, and continued monitoring by the National Antimicrobial Resistance Monitoring System (NARMS). These are all applicable to the proposed use of lincomycin in swine as described above.

Decision Statement

The Agency's integration of the degree of risk derived from the three individual assessments (low, medium, and highly important) gave an overall risk estimation of *medium*. The conditions of use are compatible with the Agency's risk management strategies for a Category 2 drug, corresponding to the estimated medium risk. Further, post-approval monitoring may be achieved from the testing of a surrogate antimicrobial (clindamycin) in the current NARMS program.

B. Impact of Residues on Human Intestinal Flora

No further information or data on the effects of lincomycin residues on human intestinal flora were necessary for this supplemental approval. The Agency continues to rely on the acceptable daily intake (ADI) value established and reported by the Joint FAO/WHO Expert Committee on Food Additives[1,2]. Further, the Agency concludes that the codified ADI of 25 mg/kg body weight/day protects against adverse effects of lincomycin residues on human intestinal flora; consequently, the ADI for lincomycin residues remains as 25 mg/kg body weight/day.

[1] http://www.who.int/foodsafety/publications/monographs/en/

[2] http://www.inchem.org/documents/jecfa/jecmono/v45je02.htm

C. Toxicology

Reassessment of the toxicological ADI was not needed for this approval. The FOI Summaries for the supplemental approvals of NADA 97-505, dated January 31, 1990, and NADA 111-636, dated January 23, 1990, contain summaries of all toxicology studies and information.

D. Establishment of the Final ADI

The final ADI is the microbiological ADI of 25 µg/kg body weight/day for total residues of lincomycin. The codified ADI is listed under 21 CFR §556.360.

E. Safe Concentrations for Total Residues in Edible Tissues

The safe concentrations of total residues of lincomycin in each edible tissue of swine are 5 ppm for muscle, 15 ppm for liver, 30 ppm for kidney and 30 ppm for fat/skin.

F. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 097-505, dated February 25, 1976, the FOI Summary for the supplemental approval of NADA 097-505, dated August 25, 1998, and the FOI Summary for the supplemental approval of NADA 034-025, dated August 25, 1998, contain a summary of residue chemistry studies for swine.

G. Analytical Method for Residues

The FOI Summary for the original approval of NADA 097-505 dated February 25, 1976, contains the analytical method summaries for LINCOMIX® 20 and LINCOMIX® 50 Type A medicated articles in swine.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to LINCOMIX® 20 and LINCOMIX® 50:

NOT FOR HUMAN USE

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Type B and Type C medicated feeds containing LINCOMIX® 20 and LINCOMIX® 50:

To report adverse effects, access medical information, or obtain additional product information, call 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 LINCOMIX® 20 and LINCOMIX® 50, when used according to the label, is safe and effective for the reduction in the severity of the effects of respiratory disease associated with *Mycoplasma hyopneumoniae* in swine. Additionally, data

demonstrate that residues in food products derived from species treated with LINCOMIX® 20 and LINCOMIX® 50 will not represent a public health concern when the product is used according to the label.

A. Marketing Status

A valid veterinary feed directive (VFD) is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of their professional practice. The decision to restrict this drug to VFD marketing status is based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately and safely use this product and (b) restricting this drug to use by or upon the order of a licensed veterinarian should help prevent indiscriminate use, which could result in violative tissue residues. In addition, reorders (refills) of veterinary feed directives issued for this VFD drug are not permitted.

B. Exclusivity

This supplemental approval for LINCOMIX® 20 and LINCOMIX® 50 qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the addition of the range of 100 to 200 grams of lincomycin per ton of complete feed associated with the indication for reduction in the severity of the effects of respiratory disease associated with *Mycoplasma hyopneumoniae* in swine.

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

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