Date of Approval: December 7, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-361

PULMOTIL AC

Tilmicosin Phosphate

Aqueous Concentrate

Swine

For the control of swine respiratory disease (SRD) associated with *Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) in groups of swine in buildings where a respiratory disease outbreak is diagnosed.

Sponsored by:

Elanco Animal Health,
A Division of Eli Lilly & Co.

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I. GENERAL INFORMATION

A. File Number

NADA 141-361

B. Sponsor

Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

Drug Labeler Code: 000986

C. Proprietary Name

PULMOTIL AC

D. Established Name

Tilmicosin phosphate

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Aqueous concentrate

G. Amount of Active Ingredient

250 mg/mL

H. How Supplied

960 mL container

I. Dispensing Status

Rx

J. Dosage Regimen

200 mg tilmicosin/L (200 ppm) for 5 consecutive days

K. Route of Administration

Oral, in drinking water

L. Species / Class

Swine

M. Indication

For the control of swine respiratory disease associated with *Pasteurella multocida* and *Haemophilus parasuis* in groups of swine in buildings where a respiratory disease outbreak is diagnosed.

For the control of swine respiratory disease associated with *Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) in groups of swine in buildings where a respiratory disease outbreak is diagnosed.

N. Effect of Supplement

This supplement provides for a new indication for the control of swine respiratory disease (SRD) associated with *Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) in groups of swine in buildings where a respiratory disease outbreak is diagnosed.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-361 dated February 13, 2014, contains dosage characterization information for swine.

B. Substantial Evidence

The effectiveness of tilmicosin phosphate for the control of swine respiratory disease (SRD) associated with *Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) was demonstrated using 1) an experimentally-induced infection model study to demonstrate that the drug has an effect (decreased lung lesions) against *M. hyopneumoniae* alone and in the presence of PRRSV, and 2) the *M. hyopneumoniae* and PRRSV prevalence data from the SRD field study (Study T5CAM0709) conducted for the original approval of PULMOTIL AC, to demonstrate that the drug is effective under field conditions for the labeled indication.

1. Induced Infection Model Study

a. Title: "Clinical Study: A model study demonstrating the effectiveness of tilmicosin phosphate (PULMOTIL AC) for controlling swine respiratory disease associated with *Mycoplasma hyopneumoniae* in swine in the presence of Porcine Reproductive and Respiratory Syndrome Virus." Study Number T5CUS140005. September 2014 to October 2014.

b. Investigator: Lyle Kesl, DVM. Veterinary Resources, Inc., Ames, IA

c. Study Design:

1) Objective: To demonstrate that tilmicosin phosphate (as PULMOTIL AC) administered to swine at 200 ppm for 5 days via drinking water

decreases lung lesions associated with *M. hyopneumoniae* alone and in the presence of PRRSV.

2) Study Animals: A total of 340 commercial crossbred pigs were enrolled in the study. Pigs were females and castrated males, approximately 3 to 4 weeks of age at arrival. The pigs were sourced from litters which were serologically negative for *M. hyopneumoniae* and PRRSV. Pigs in each infection group were housed in separate facilities.

3) Experimental Design: The study was a randomized complete block design with two infection groups and two treatment groups per infection group. Each block contained two pens (one control pen and one tilmicosin-treated pen). The pen was the experimental unit. Pigs were assigned to one of four treatment groups as shown in Table II.B.1 and Table II.B.2.

Table II.B.1. Treatment Groups – Single Infection (*M. hyopneumoniae*)

Treatment Group	Treatment	Number of Pens	Number of Pigs
TG01	0 ppm tilmicosin phosphate	15	90 study pigs 10 sentinel pigs
TG02	200 ppm tilmicosin phosphate	15	90 study pigs 10 sentinel pigs

Table II.B.2. Treatment Groups – Co-Infection (*M. hyopneumoniae and PRRSV*)

Treatment Group	Treatment	Number of Pens	Number of Pigs
TG03	0 ppm tilmicosin phosphate	10	60 study pigs 10 sentinel pigs
TG04	200 ppm tilmicosin phosphate	10	60 study pigs 10 sentinel pigs

4) Challenge Administration: Pigs in the single infection group received 10 mL of *M. hyopneumoniae* inoculum by endotracheal administration. Pigs in the co-infection group received 10 mL of *M. hyopneumoniae* inoculum by endotracheal administration and 2 mL of PRRSV inoculum by intranasal administration. The *M. hyopneumoniae* and PRRSV challenge strains used in the study were shown to be representative of current U.S. strains.

5) Drug Administration: The test article was PULMOTIL AC water soluble concentrate (250 mg tilmicosin phosphate per mL), administered in drinking water at 200 mg tilmicosin phosphate/L (200 ppm). Non-medicated water was used as the control article. Treatment and control group water was provided *ad libitum* for 5 days. Medicated water was prepared fresh for each of the five treatment days.

6) Measurements and Observations: Pigs were acclimated to the facility for three weeks, and then were assigned to infection group, pen, and

treatment group. During the acclimation, treatment, and post-treatment period, pigs were observed twice daily for general health and facility/equipment conditions. Body weights, feed intake, and water intake were measured during the study.

At specified intervals following administration of the challenge, pre-selected sentinel pigs were euthanized and the lung lesion percentage was calculated to determine the start of treatment for each infection group. The percent of lesions in each lung lobe was recorded and an overall percentage was calculated for each pig. Treatment was initiated when the average lung lesion percentage of the sentinel pigs was at least 5%.

After the 5-day treatment period and a 4-day post-treatment period, all pigs were euthanized and necropsied to determine lung lesion percentage. Lung lesion percentage was calculated as the sum of the lung lesion percentage observed in each lobe multiplied by the approximate volume that each lobe contributes to the entire lung volume (left cranial lobe – 20%, left caudal lobe – 27.5%, right cranial lobe – 10%, right middle lobe – 10%, right caudal lobe – 27.5%, and accessory lobe – 5%).

7) Statistical Analysis: The percentage of total lung volume having lesions was analyzed using a linear mixed model with treatment as a fixed effect and block as a random effect. The infection groups were analyzed separately. The difference between the tilmicosin phosphate and control groups was tested using a two-sided test with alpha=0.05.

d. Results: For both the single-infection and co-infection groups, pigs administered tilmicosin phosphate had a statistically significantly different percentage of lung lesions compared with the control group.

Table II.B.3. Lung Lesion Percentage Results

Treatment Group	Control (0 ppm)	Tilmicosin phosphate (200 ppm)	P-value*
Co-infection	43.04% (1.94)#	31.74% (1.94)	0.0004
Single infection	28.26% (1.56)	21.01% (1.56)	0.0050

Least Squares Mean (Standard Error)
* P-value is from mixed model analysis with fixed effect of treatment (0 ppm vs. 200 ppm) and random effect of block

e. Adverse Reactions: There were no test article-related adverse reactions in the study.

f. Conclusions: This study demonstrates that tilmicosin phosphate (as PULMOTIL AC) administered to swine at 200 ppm for 5 days via drinking water decreased lung lesions associated with M. hyopneumoniae and with M. hyopneumoniae in the presence of PRRSV.

2. SRD Field Study T5CAM0709

A multi-site field study was conducted to demonstrate the effectiveness of tilmicosin phosphate (as PULMOTIL AC) for the control of SRD when administered at 200 mg tilmicosin phosphate/L (200 ppm) in water for 5 consecutive days. This study was previously summarized in the Freedom of Information (FOI) Summary for the original approval of NADA 141-361 dated February 13, 2014.

To confirm the presence of *M. hyopneumoniae*, lung samples from pigs in Study T5CAM0709 were screened with a quantitative polymerase chain reaction (PCR) test. Of the 1,079 samples tested, 120 (11%) were PCR positive for *M. hyopneumoniae*. A total of 33 *M. hyopneumoniae* isolates were successfully grown in culture from the *M. hyopneumoniae*-positive PCR samples. Over 90% of study pigs across all sites were PRRSV-positive. The data demonstrate that tilmicosin phosphate was effective under field use conditions for the control of SRD associated with *M. hyopneumoniae* in the presence of PRRSV.

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 141-361 dated February 13, 2014, contains a summary of target animal safety studies for swine.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

CVM did not require additional information for microbial food safety (antimicrobial resistance) for the addition of the pathogens "*Mycoplasma hyopneumoniae* in the presence of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV)" to the indication of PULMOTIL AC (200 mg/L for 5 days) for the control of swine respiratory disease (SRD) in growing swine. The evaluation of the risk of the use of PULMOTIL AC, as outlined in the FOI Summary for NADA 141-361 dated February 13, 2014, addressed factors associated with the inclusion of *Mycoplasma hyopneumoniae* in the presence of PRRSV in the indication of this product. Further definition of the claim by addition of specific organisms helps ensure accurate use and promotes safety with regards to resistance development.

Decision Statement

CVM did not require additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for the original approval of NADA 141-361 dated February 13, 2014, contains a summary of all information used to assess the risk to microbial food safety (antimicrobial resistance).

B. Impact of Residues on Human Intestinal Flora

CVM did not require additional information for the impact of residues on human intestinal flora for this supplemental approval. The FOI Summary for the original

approval of NADA 141-361 dated February 13, 2014, contains a summary of all information used to assess the impact of residues on human intestinal flora.

C. Toxicology

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this supplemental approval. The FOI summary for the original approval of NADA 140-929 dated March 24, 1992, and the original approval of NADA 141-361 dated February 13, 2014, contains a summary of all toxicology studies and information.

D. Establishment of the Final ADI

The final ADI is the microbiological ADI of 25 micrograms per kilogram of body weight per day derived from *in vitro* minimum inhibitory concentration (MIC) data. The codified ADI is listed under 21 CFR 556.735.

E. Safe Concentrations for Total Residues

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

F. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-361 dated February 13, 2014, the original approval of NADA 141-064, dated December 17, 1996, and the supplemental approval of NADA 141-064, dated February 2, 1999, contain summaries of residue chemistry studies for swine.

G. Analytical Method for Residues

The FOI Summary for the original approval of NADA 141-064 dated December 17, 1996, contains the analytical method summaries for tilmicosin in swine.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PULMOTIL AC:

WARNING

Exposure to tilmicosin in humans has been associated with chest pain, increased heart rate, dizziness, headache, and nausea. Death has been reported following ingestion or injection of tilmicosin.

Avoid ingestion. Avoid direct skin and eye contact. In case of human exposure, call 1-800-722-0987 and consult a physician immediately.

NOTE TO THE PHYSICIAN:

The cardiovascular system is the target of toxicity and should be monitored closely. The primary cardiac effects are tachycardia and decreased contractility. Cardiovascular toxicity may be due to calcium channel blockade.

See User Safety Warnings for additional information.

USER SAFETY WARNINGS:

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. SEE BOXED WARNING AND NOTE TO THE PHYSICIAN FOR ADDITIONAL INFORMATION. Wear overalls, impervious gloves, and eye protection when mixing and handling the product. Wash hands after handling the product. Wash affected parts if skin contact occurs. If accidental eye contact occurs, immediately rinse thoroughly with water.

To report suspected adverse events, for technical assistance, or to obtain a Material Safety Data Sheet (MSDS), call 1-800-428-4441.

Note to the Physician:

The cardiovascular system is the target of toxicity and should be monitored closely. Cardiovascular toxicity may be due to calcium channel blockade. In dogs, administration of intravenous calcium offset tilmicosin-induced tachycardia and negative inotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by tilmicosin injection in dogs. ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of tilmicosin injection in dogs. Epinephrine potentiated lethality of tilmicosin injection in pigs. This antibiotic persists in tissues for several days.

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 PULMOTIL AC, when used according to the label, is safe and effective for the control of swine respiratory disease associated with *Mycoplasma hyopneumoniae* in the presence of PRRSV in groups of swine in buildings where a respiratory disease outbreak is diagnosed. Additionally, data demonstrate that

residues in food products derived from species treated with PULMOTIL AC will not represent a public health concern when the product is used according to the label.

A. Marketing Status

Labeling restricts this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to control swine respiratory disease; and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

B. Exclusivity

This supplemental approval for PULMOTIL AC 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 indication "for the control of swine respiratory disease associated with *Mycoplasma hyopneumoniae* in the presence of PRRSV in groups of swine in buildings where a respiratory disease outbreak is diagnosed."

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.