Date of Approval: February 13, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-361

PULMOTIL AC

Tilmicosin Phosphate

Aqueous Concentrate

Swine

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.

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.

II. EFFECTIVENESS

A. Dosage Characterization

Two studies (Study T5C319601 and Study T5C319602) were conducted in Nebraska in 1996 to determine which tilmicosin dose(s) were effective, prior to conducting pivotal effectiveness studies. The studies were staggered two days apart, and used the same procedures and the same animal source. Study pigs were females and castrated males, approximately 6 to 12 weeks of age, weighing approximately 30 to 80 lbs. On the day of arrival (Day 0), pigs were allocated as seeder pigs (60 pigs per study), replacement pigs (10 pigs per study), or to one of four treatment groups– non-medicated control, or tilmicosin at 100, 200, or 300 mg/L in drinking water (120 pigs per study). Assigned treatments were administered for 5 consecutive days, beginning with the day pigs were exposed to the seeder pigs (Day 4). On Day 7, after three days of exposure to the study pigs, seeder pigs were removed and euthanized.

Study pigs were observed daily for mortality, clinical signs of swine respiratory disease (SRD) (evaluated as a composite score of attitude, abdominal appearance, appearance of the eyes, hydration status, and respiration), rectal temperature, body weight, and water consumption. Study pigs were euthanized on Day 14 for lung lesion evaluation and culture.

For all three tilmicosin doses, mortality, clinical SRD scores, rectal temperature, body weight gain, and mean lung lesion percentage were improved compared to the untreated controls, and 300 mg/L was more effective than 100 mg/L. Water consumption decreased in all groups when treatment started, but returned to normal by the second day of treatment. A dosage of 200 mg/L was chosen for further evaluation.

B. Substantial Evidence

Natural Infection Field Study

a. Title: "Clinical Study: An Efficacy Study with PULMOTIL AC for the Control of Naturally Occurring Swine Respiratory Disease." Study T5CAM0709. May 2011 to August 2011.

b. Investigators and Study Locations:

Lyle Kesl, DVM, PhD. Veterinary Resources, Inc., Ames, IA
Kelly Lechtenberg, DVM, PhD. Midwest Veterinary Services, Inc., Oakland, NE
Teresa Schieber, DVM. Central States Research Centre, Inc., Oakland, NE
Terry TerHune, DVM, PhD. HMS Veterinary Development, Inc., Tulare, CA
Jeffrey Chewning, PhD. Swine Research Services, Inc., Springdale, AR
Ryan Saltzman, DVM. Veterinary Resources, Inc., Ames, IA

c. Study Design:

1) *Objective*: To demonstrate the effectiveness of tilmicosin administered in drinking water for the control of SRD associated with *Actinobacillus pleuropneumoniae*, and/or *Pasteurella multocida*, and/or *Haemophilus parasuis*, and/or *Actinobacillus suis*.

2) *Study Animals*: At each site, a total of 180 female and castrated male growing pigs (160 enrolled pigs plus 20 sentinel pigs) were used for the study. Pigs were 4 to 11 weeks old at receipt; pigs within a site did not vary by more than 3 weeks of age. The strains (breeds) used were commercial-type pigs available in the geographic area. Pigs were sourced from commercial swine facilities and were individually tagged with duplicate uniquely numbered ear tags.

The candidate group was observed at least twice per day beginning at receipt for signs of SRD. When at least 15% of the candidate group was classified as clinically affected (defined under Measurements and Observations below), pigs were allocated to pens and treatment group. Pigs classified as clinically affected were randomly assigned to pens first, followed by the remaining pigs, so that one clinically affected pig and seven non-affected pigs were assigned to each study pen. Sentinel pigs were sacrificed prior to or on Day 0 to isolate organisms of interest for the study.

3) *Treatment Groups*: The test article was PULMOTIL AC water soluble concentrate (250 mg tilmicosin per mL), administered in drinking water at 200 mg tilmicosin/L. Non-medicated water was used as the control article. At each site, 10 pens (80 pigs) were assigned to each of the two treatments. Across the study, 480 pigs were enrolled in the tilmicosin group, and 480 pigs were enrolled in the control group.

4) *Drug Administration*: Treatment and control group water was initiated following allocation on Day 0 and was provided *ad libitum* for 5 days. Medicated water was prepared fresh for each of the five treatment days.

5) *Measurements and Observations*: After arrival, pigs were observed at least twice per day to determine their health status. Pigs that 1) were found dead and were diagnosed with SRD, or 2) had a depression score ≥ 2 (on a scale from 0 [normal] to 3 [severe]) and a respiratory score ≥ 2 (on a scale from 0 [normal] to 3 [severe]) and a rectal temperature of ≥ 104.5 °F were considered clinically affected. Pigs considered moribund were euthanized and necropsied.

During the treatment period (Days 0 to 5), the weight of water dispensed and disposed of for each pen was recorded daily. Individual pig weights were recorded on Day 0, Day 5 (end of treatment period), and Day 9 (end of post-treatment period). Feed weights were recorded as feed was issued or removed from Day 0 to Day 9, and also on Day 5 (all pens). From Day 0 through Day 9, pigs were observed at least once daily to determine general health status (survival and general condition). On Day 9, all remaining pigs were weighed, scored clinically (respiration and depression), and had their rectal temperature taken. All remaining pigs

were euthanized on Day 10. A sample of lung tissue and a lung swab was collected from each pig at necropsy, and cultured to determine the presence of *A. pleuropneumoniae*, *P. multocida*, and *H. parasuis*. The identification of isolates of *H. parasuis* was confirmed using a validated polymerase chain reaction (PCR) method.

d. Statistical Analysis: The study was a complete randomized block design using pen as the experimental unit. The primary variable for determining effectiveness was treatment success. Each pig was classified as a success or failure on Day 9. Treatment success was defined as a pig that had a rectal temperature < 104.5 °F, and a respiratory score = 1 or 0, and a depression score = 1 or 0. Pigs that did not meet the success criteria were considered treatment failures. Pigs removed during the study or that were found dead and diagnosed with SRD were also classified as treatment failures.

   Analysis of treatment success, pooled across all six sites, was conducted using a generalized linear mixed model and assuming a binomial distribution and using a logit link. Treatment was the fixed factor, and site, treatment by site interaction, and block within site were the random factors. A two-sided comparison of tilmicosin versus control was conducted at a 0.05 significance level.

e. Results: Twelve pigs that were removed from the study for non-SRD illness or injury were excluded from the effectiveness analysis. A statistically significantly higher (p = 0.0118) success rate (based on back-transformed least squares means) was detected for the treated group (275/473, 58.64%) compared to the control group (230/475, 47.89%). A total of 127 isolates of *P. multocida* and 506 isolates of *H. parasuis* were identified. No isolates of *A. pleuropneumoniae* were isolated from study samples.

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

g. Conclusions: This study demonstrates that tilmicosin, administered as PULMOTIL AC, was effective for the control of SRD associated with *P. multocida* and *H. parasuis* when administered at 200 mg tilmicosin/L in drinking water (200 ppm) for 5 consecutive days.

III. TARGET ANIMAL SAFETY:

The FOI Summary for the original approval of NADA 141-064 [PULMOTIL (tilmicosin) 90 Type A medicated article] dated December 17, 1996, contains a summary of target animal safety studies for swine.

The target animal safety of PULMOTIL AC was established by providing a pharmacokinetic bridge to PULMOTIL 90 Type A medicated article (NADA 141-064). Safety was confirmed using a plasma and tissue drug level approach, comparing the drug exposure of PULMOTIL AC to PULMOTIL 90 Type A medicated article (NADA 141-064).

An additional study was conducted to evaluate the tolerance of swine to various concentrations of PULMOTIL AC. Further, hydration and water consumption were evaluated during the control of SRD effectiveness field study.

A. Pharmacokinetic Study

1. Title: "Tilmicosin Soluble Pharmacokinetic Study in Pigs Following Oral Administration in Drinking Water." Study ELA-96-05. September 1996 to October 1996.

2. Investigator: A. R. Peters *et al*., Royal Veterinary College, United Kingdom

3. Study Design:

   a. *Objective*: To determine serum and lung tissue concentrations of tilmicosin in pigs after administration of 0, 100, 200, or 300 mg tilmicosin/L in the drinking water for five consecutive days.

   b. *Experimental Design:* Thirty-six, 10- to 12-week old, healthy Large White pigs, weighing approximately 35 kg, were enrolled in this study. In Phase 1 of the study, tilmicosin was administered to 16 pigs (4 pigs/group) at concentrations of 0 (control), 100, 200, or 300 mg/L (0.5X, 1X, or 1.5X the labeled dose) in drinking water for five consecutive days. Jugular venous blood samples were collected from surgically-placed intravenous catheters at prescribed intervals from 0 hours to 168 hours after the beginning of treatment to evaluate tilmicosin blood concentrations. The control group and the 200 mg/L group were euthanized at 168 hours after the start of treatment to evaluate lung tissue concentrations.

      In Phase 2 of the study, tilmicosin was administered to 20 pigs at a concentration of 200 mg/L in the drinking water for five consecutive days. Pigs were euthanized in groups of four at 6, 24, 72, 96, and 120 hours after the start of treatment to evaluate lung tissue concentrations.

      Water consumption was evaluated throughout the study (Phase 1 and Phase 2). Serum samples and homogenized lung samples were assayed for tilmicosin by a high-performance liquid chromatography (HPLC) method, which was validated to a limit of quantification (LOQ) of 0.1 µg/mL.

4. Results: During the Phase 1 treatment period, group mean daily water intakes were markedly lower in the 200 and 300 mg/L groups, compared to the control group. Group mean water intake for the day following the last treatment (after return to non-medicated water) increased by approximately 1.5 L in the 200 and 300 mg/L groups reaching the pre-treatment water-intake levels. Water intake was similarly reduced in Phase 2, and returned to or surpassed pre-treatment levels on the day following removal of tilmicosin from drinking water.

   In Phase 1, serum tilmicosin levels of were very low in all dose groups. In the 100 and 200 mg/L groups, tilmicosin levels were below the LOQ at all points during the study. In the 300 mg/L group, serum tilmicosin levels were below the LOQ for most time points. Therefore, the serum level data for tilmicosin in drinking water were unsuitable for any drug concentration analyses.

Tilmicosin concentrations in lung tissue from Phase 2 of the study ranged from an average of 0.05 (±0.08 standard deviation [SD]) µg/g of lung tissue at 6 hours after the start of treatment to a peak of 0.58 (±0.095) µg/g of lung tissue at 120 hours after the start of treatment. Lung tissue levels of tilmicosin from this study were used for comparing drug exposure following administration of therapeutic doses of tilmicosin in feed and drinking water, as described below.

B. Comparison of Lung Tissue Concentrations Following Administration in Drinking Water or Medicated Feed

When the results of Study ELA-96-05 are compared to data generated with medicated feed containing PULMOTIL 90 Type A medicated article (NADA 141-064, Study T5CAX9302), the data demonstrate that the blood and tissue levels of tilmicosin when administered to pigs at 200 mg/L (200 ppm) in drinking water were consistently lower than when tilmicosin was administered to pigs at 181 g/ton (200 ppm) in feed. Both feed and water administration resulted in tilmicosin serum concentrations below the LOQ when administered at 200 ppm (181 g/ton in feed). The results for the lung tissue concentrations are shown in Table 1.

Table 1. Comparison of mean tilmicosin lung tissue concentrations (µg/g)* following administration to pigs in medicated water (Study ELA-96-05) or medicated feed (Study T5CAX9302).

Time after start of treatment (hours)	Medicated water 200 mg/L (ppm)	Medicated feed 200 ppm	Medicated feed 400 ppm
6	0.05 (0.08)**	-	-
24	0.18 (0.06)	-	-
48	-	0.73 (0.19)	1.11 (0.24)
72	0.52 (0.12)	-	-
96	0.38 (0.16)	1.11 (0.55)	2.29 (0.27)
120	0.58 (0.10)	-	-
168	0.30 (0.19)	0.59 (0.19)	2.24 (0.88)

* Dashes indicate that concentrations were not measured at these time points.
** Numbers in parentheses represent the standard deviation (SD).

The data demonstrate that the overall tilmicosin exposure in pigs is lower when tilmicosin is administered at 200 mg/L (200 ppm) in drinking water than when tilmicosin is administered at 181 g/ton (200 ppm) in feed, the lowest concentration approved for the use of PULMOTIL 90 Type A medicated article in swine. Therefore, a margin of safety is established for tilmicosin administered at 200 mg/L in drinking water.

C. Tolerance Study

1. Title: "Tilmicosin: A Tolerance Study in Swine." Study 158644. August 1996 to September 1996.

2. Investigator: C. L. McLean *et al*., Inveresk Research, Scotland

3. Study Design:

   a. *Objective*: To investigate the tolerance of pigs to tilmicosin at the labeled concentration in drinking water (1X) and at exaggerated concentrations (2X and 3X).

   b. *Experimental Design:* Twenty, approximately 12-week old, healthy Large White/Landrace crossbred pigs, weighing approximately 20 kg, were enrolled in this study. Tilmicosin was administered in drinking water to three groups of four pigs (2 male and 2 female) for five consecutive days at concentrations of 200, 400, or 600 mg/L (1X, 2X, or 3X the labeled dose). A fourth group of four pigs received tilmicosin in drinking water for 10 consecutive days at a dose rate of 200 mg/L. A control group of four pigs received non-medicated drinking water.

   c. *Measurements and Observations:* Daily water consumption was measured throughout the study. Pigs were observed for any signs of intolerance during the treatment period and for two weeks after the last dose. Pigs were then euthanized and subjected to gross pathological investigation by a veterinary pathologist.

4. Results: Water consumption results for the treatment period are shown in Table 2.

Table 2. Group mean water consumption for the treatment period.

Group	Mean Water Consumption (g)
200 mg tilmicosin/L, 5 consecutive days	2427.2
400 mg tilmicosin/L, 5 consecutive days	1641.0
600 mg tilmicosin/L, 5 consecutive days	2066.2
200 mg tilmicosin/L, 10 consecutive days	2590.2
control	3302.8

Mean group water consumption was lower in all tilmicosin-treated groups compared to the control group. Mean group water consumption was markedly decreased in the 400 and 600 mg/L groups compared to the control group. In the 400 mg/L group, two pigs had clinical signs attributed to reduced water intake. One of these two pigs was observed to be "very dull and unresponsive" on Day 3 and was subsequently offered fresh water instead of tilmicosin-medicated water, after which it made a complete recovery. The second affected pig exhibited similar signs, although to a lesser degree, and completed the treatment period without intervention. In the 600 mg/L group, one pig showed signs of dullness and unresponsiveness throughout the treatment period; this pig completed the treatment period without intervention. A second pig in the 600 mg/L group showed neurological signs (twitching, circling, head rubbing) attributed to severe dehydration on Day 2.

This pig stopped drinking altogether, even when fresh water was administered. Its condition did not improve and it was euthanized.

No treatment-related lesions were found in any pigs at necropsy.

5. Conclusion: Pigs treated with PULMOTIL AC showed decreased water consumption in all treatment groups. Decreased water consumption at higher doses resulted in neurological signs associated with severe dehydration. The study also demonstrated that the potential for toxicity associated with over consumption is minimal due to palatability and subsequent product refusal.

D. Hydration and Water Consumption Evaluation from the SRD Effectiveness Field Study

Hydration and water consumption were evaluated during the control of SRD effectiveness field study (Study T5CAM0709) described above. Total water intake from Day 0 through Day 5 was evaluated for five of the six study sites (water intake was not evaluated at one site because of a deviation). There was no statistically significant difference in total water consumption (by pen) between the PULMOTIL AC-treated pigs (82.18 kg) compared to the control pigs (75.48 kg, $p = 0.093$).

At one site, two pigs from each pen (40 pigs total [20 pigs from each treatment group]) were included in the hydration evaluation. Prior to receiving treatment, and again at the end of the treatment period, a physical examination was performed by a veterinarian and blood samples were collected from each pig. Blood samples were analyzed for hematocrit, total protein, creatinine, and blood urea nitrogen.

No pigs were classified as having clinical evidence of dehydration on Day 0 or Day 5 based on the physical examination. Although both groups had individual values for each laboratory variable that were outside the normal reference range, collectively there were no clinically relevant changes to indicate dehydration.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

Microbial Food Safety (Antimicrobial Resistance):

Microbial food safety (antimicrobial resistance) information for tilmicosin phosphate was evaluated using a qualitative risk assessment procedure. The dosage regimen evaluated was 200 mg/L tilmicosin phosphate in the drinking water of swine for 5 consecutive days. The indication associated with this dosage regimen is, "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."

The sponsor provided a complete, qualitative microbial food safety risk assessment for review by the Agency. The qualitative microbial food safety risk assessment included 1) a *release assessment* to describe the probability that tilmicosin phosphate and its use in swine will result in the emergence of

macrolide-resistant (or other drug-resistant) bacteria or macrolide resistance determinants in treated swine under proposed conditions of use; 2) an *exposure assessment* to describe the likelihood of human exposure to macrolide-resistant (or other drug-resistant) bacteria or macrolide resistance determinants through consumption of edible products from treated swine; and 3) a *consequence assessment* to describe potential human health consequences arising from exposure to macrolide-resistant (or other drug-resistant) bacteria or macrolide resistance determinants by considering the human medical importance of antimicrobial drugs used in the treatment of human infectious diseases.

After review of the sponsor's complete, qualitative microbial food safety risk assessment, the Agency determined that the risk of development of transferable macrolide resistance elements from this use of tilmicosin phosphate in swine is high, and the risk of human exposure to macrolide resistant microbes resulting from this use of tilmicosin phosphate is medium. Macrolides are ranked as critically important drugs in human medicine; therefore, by default, the consequence assessment yields a high ranking. The overall risk estimation is derived to be high. The conditions of use are compatible with the Agency's risk management strategies associated with a product having an overall risk estimation of high – the product will be marketed by prescription only (Rx), can only be administered to individual or limited groups of swine in buildings experiencing an outbreak of SRD, and monitoring for macrolide resistance within FDA's National Antimicrobial Resistance Monitoring System continues.

Decision Statement:

The Agency's integration of the degree of risk derived from the three individual assessments (high/medium/high) gave an overall risk estimation of high. The Agency thinks the labeled conditions of use are compatible with its risk mitigation strategies for a drug with an estimated high risk for influencing antimicrobial resistance. Further, post-approval monitoring may be achieved from testing of surrogate antimicrobials (erythromycin and azithromycin) in the current NARMS program.

B. Impact of Residues on Human Intestinal Flora:

The safety of tilmicosin-related residues in edible animal tissues was previously assessed for potential effects on the intestinal flora of human consumers in association with an application for tilmicosin injectable use in cattle by this firm. A complete description of the effects of tilmicosin residues on human intestinal flora can be found in the Freedom of Information Summary associated with a supplemental approval to NADA 140-929 [MICOTIL (tilmicosin) 300 injectable solution, FOI Summary dated December 30, 2009], where a stepwise approach was followed. A microbiological acceptable daily intake (mADI) of 25 µg/kg body weight *per* day was determined. Concerns for impact on human intestinal flora and establishment of a mADI under NADA 140-929 were assessed and determined based on residue concentrations present in injection site muscle tissues of cattle treated with an injectable dosing regimen.

For the current application, the firm assessed the effects of tilmicosin residues on human intestinal flora associated with residues in edible tissues of swine treated with an oral (drinking water) regimen.

Tissue residue data from swine medicated with 200 ppm tilmicosin in drinking water (Elanco Animal Health Study # T5C699601, described in the *Residue Chemistry* section of this FOI Summary) demonstrated that following seven days of withdrawal time, liver had the highest residue concentration, at an average of 0.32 ppm. This residue concentration represents a worst case scenario for human consumption, and provides the most conservative approach for evaluating the safety of tilmicosin with respect to effects on human intestinal flora. The assessment specific to the current application revealed the following key findings:

1. Expected residues in edible tissues from tilmicosin treated swine at the proposed withdrawal time fall well below the confirmed mADI and tolerance for the compound (25 µg/kg body weight *per* day and 1.2 ppm, respectively);

2. Amounts of biologically active tilmicosin that could be ingested by an average person as a result of consuming edible tissues under proposed conditions of use are well below the tilmicosin minimum inhibitory concentration (MIC) of concern described in the FOI Summary for NADA 140-929. Therefore, the concentration of biologically active tilmicosin in the human colon following consumption of edible tissues derived from treated swine is too low to cause a disruption of colonization barrier.

In summary, concern for effects on human intestinal flora of tilmicosin residues in edible tissues of swine treated for 5 days with 200 mg/L of tilmicosin in drinking water, followed by a 7-day withdrawal period, is minimal. The human intestinal flora of consumers of food products derived from treated swine are protected by the already established mADI for the compound.

Thus, the mADI is 25 µg/kg body weight *per* day.

C. Toxicology:

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

D. Assignment 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 (edible tissues and injection sites, if applicable):

The safe concentrations of total tilmicosin residues 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:

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Studies

Summaries of total residue and metabolism information for tilmicosin administered orally to swine are included in the FOI Summaries for the original approval of NADA 141-064, dated December 17, 1996, and the supplemental approval of NADA 141-064, dated February 2, 1999.

b. Comparative Metabolism Study

Information to support comparative metabolism for tilmicosin in swine and the laboratory model species is included in the FOI Summaries for the original approval of NADA 141-064, dated December 17, 1996, and the original approval of NADA 140-929, dated March 24, 1992.

c. Study to Establish Withdrawal Period

Tissue Residue Depletion Study

The following pivotal study was conducted to permit the decision on the withdrawal period.

Study T5C699601-- "Tissue Residue Decline Study in Swine Medicated with 200 ppm Tilmicosin in Drinking Water"

Objectives
The purpose of the study was to determine the concentration of parent tilmicosin residue in swine liver at various time points following administration of tilmicosin in swine drinking water for five consecutive days.

Study Dates
Initiation - February 11, 1997
Completion - July 2, 1997

Study Sponsor
Elanco Animal Health
A Division of Eli Lilly & Company
Greenfield, IN 46140

Test Substance
Tilmicosin Aqueous

Test Animals
Thirty crossbred swine, weighing approximately 20 kg at the start of the study, were randomly assigned to 5 groups (the control and 4 tilmicosin treated groups) of three males and three females *per* group.

Study Design

The treatment was for a five-day period, during which time the pigs in the tilmicosin treated groups were allowed *ad libitum* access to 200 mg tilmicosin/L drinking water solution. The average tilmicosin dose intake was 14.8 mg/kg body weight/day for the treated groups. The animals were euthanized by captive bolt followed by exsanguination at a zero-day (Group 01), 7-day (Group 02), 14-day (Group 03) or 21-day (Group 04) withdrawal after cessation of the treatment. The control animals were euthanized with Group 01 animals.

The edible tissues were collected from each pig and analyzed for parent tilmicosin residue concentration by a high performance liquid chromatography (HPLC) method.

Results

Table 3. Mean parent tilmicosin residue concentrations (µg/g) in edible tissues after treatment with 200 ppm tilmicosin in drinking water.

Withdrawal (Day)	Animal No.	Kidney	Liver	Fat	Muscle
0	6	3.90	2.90	0.21	0.43
7	6	0.22	0.32	*	*
14	6	0.057	0.075	*	*
21	6	*	≤ 0.027	**	**

*No mean value was calculated because more than half of the animals in this withdrawal group had values below the limit of quantitation of 0.025 µg/g.

** Tissues not assayed.

Conclusion

The calculated statistical tolerance limit for parent tilmicosin residue in liver for 99% of the population at 95% confidence is consistent with assigning a 7-day withdrawal period for the use of 200 ppm tilmicosin in drinking water of swine for 5 days.

2. Target Tissue and Marker Residue

The target tissue for residue monitoring is liver and the marker residue is parent tilmicosin.

3. Tolerances

The tolerance for parent tilmicosin in liver is 7.5 ppm and the tolerance for parent tilmicosin in muscle is 0.1 ppm (21 CFR 556.735).

4. Withdrawal Period

A 7-day withdrawal is assigned.

G. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-064 dated December 17, 1996, contains a summary of the analytical method 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 *Pasteurella multocida* and *Haemophilus parasuis* 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: 1) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to control swine respiratory disease; and 2) 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:

PULMOTIL AC, as approved in our approval letter, 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 safety or effectiveness of PULMOTIL AC.

C. Patent Information:

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