Date of Approval Letter: November 24, 2004

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-064

PULMOTIL 90 (tilmicosin phosphate) Type A Medicated Article

To allow for use in female breeding swine for the existing indication "For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*."

Sponsored by:

Elanco Animal Health

1. GENERAL INFORMATION:

a.	File Number:	NADA 141-064
b.	Sponsor:	Elanco Animal Health A Division of Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
c.	Established Name:	Tilmicosin phosphate
d.	Proprietary Name:	PULMOTIL 90
e.	Dosage Form:	Type A medicated article
f.	How Supplied:	20.0 lb (10 kg) bags
g.	How Dispensed:	Veterinary Feed Directive (VFD)
h.	Amount of Active Ingredients:	90.7 g per lb (200 g per kg)
i.	Route of Administration:	Oral, in the feed
j.	Species/Class:	Swine
k.	Recommended Dosage:	To be fed continuously at 181 to 363 g/ton (200 to 400 ppm) of Type C medicated feed as the sole ration for a 21-day period, beginning approximately 7 days before an anticipated disease outbreak
l.	Pharmacological Category:	Antibiotic
m.	Indication:	For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.
n.	Effect of Supplement:	To allow for use in female breeding swine for the existing indication "For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*."

2. EFFECTIVENESS:

No new effectiveness data were required for this supplement to NADA 141-064 (Original approval date December 27, 1996) and this supplement did not require review of the original effectiveness data for this product.

3. TARGET ANIMAL SAFETY:

a. Type of Study: The study is a target animal reproduction safety study in first and second parity female pigs. The dams and piglets were observed for any adverse effects and reproductive performance was measured.

b. Name and Address of Study Director:

J.M. Buck, M.S.
Elanco Animal Health
2001 W. Main Street
Greenfield, IN

c. General Design of the Investigation:

(1) *Purpose of the study*: To determine the effects of PULMOTIL when continuously fed to reproducing females at 1200 ppm immediately after the first farrowing, during the first lactation, breeding, gestation, second farrowing, and second lactation.

(2) *Test animals*: Crossbred, white bloodline gilts (11 months) and sows (16 months)

(3) *Dosage form*: A Type A Medicated Article containing 200 grams of tilmicosin per kilogram was used to make a Type C Medicated Feed containing 1200 ppm of tilmicosin. The Type A Medicated Article is the marketed form of PULMOTIL.

(4) *Route of administration*: Oral in the diet.

(5) *Treatment Groups*: Two treatment groups of 40 animals each (20 gilts pregnant with first parity upon arrival and 20 sows pregnant with second parity upon arrival for each treatment group). One group was used as an untreated control and was fed a basal diet. The second group was fed a basal diet fortified with tilmicosin at a dose of 1200 ppm.

Treatment Group	PULMOTIL (PPM)	Number of Pigs	
		First Parity	Second Parity
Treated	1200	20	20
Control	0	20	20

(6) *Study Duration*: Medicated feed was fed to each female for approximately six months (time for each female from the first on-study farrowing to the end of the second on-study lactation).

(7) *Variables*: Twice daily clinical observations, mortality, body weight, feed consumption, gross necropsy, histopathology, conception/pregnancy rate, farrowing parameters (total born, total born alive, number of stillborn, number of mummies, birth weight), piglet survival at weaning, and weaning weight.

d. Results:

No clinical signs of toxicity were observed in the dams or the piglets when the dams were fed three times the highest intended use level of PULMOTIL. No pathological signs of toxicity were evident in dams and piglets that died or were euthanized on study and were examined for gross or microscopic lesions. Statistically, no effects were detected ($P \geq 0.1066$) on the reproductive variables of conception and pregnancy rate, or in dam weight change and feed intake. Also, no statistically significant differences were identified in the following piglet variables: average litter weight of live pigs/dam at birth, average daily weight gain per piglet at weaning, number of piglets farrowed, number of piglets born alive, number of piglets weaned, number of piglets that died after being born alive, number of piglets euthanized, number of piglets laid on, number of piglets stillborn or number of piglets mummified, between treated and control groups. The only differences detected were in average live piglet birth weight (p-value < 0.0036) and average piglet weaning weight (p-value < 0.0652) for piglets from dams receiving PULMOTIL compared to control animals. Upon investigation, the data showed that the weight differences for average live piglet birth weight and average piglet weaning weight were mainly attributable to smaller litter sizes resulting in larger piglets for the controls. The control group had 9 of 32 litters with 5 or less piglets and the treated group had 4 of 36 litters with 5 or less piglets. The average piglet body weights at birth and weaning for the control group, 1.78 and 7.44 kg, respectively, and the PULMOTIL treated group, 1.61 and 6.90 kg, respectively, were similar to body weights reported in the literature. Table 3.1 summarizes the results.

Table 3.1 Reproductive Safety Variables – Trial T5CVX9701

Variable	Treatment		Treatment	
	0 ppm	1200 ppm	0 ppm	1200 ppm
	Mean	Mean	SD[a]	SD
Piglet Farrowing Weight	1.78	1.61	0.28	0.24
Litter Weight per sow	13.1	12.0	4.6	3.3
Weaning Weight	7.44	6.90	1.22	1.20
Weaning Piglets ADG	0.271	0.255	0.049	0.049
Average Total Piglets Farrowed/sow	9.8	9.8	4.5	3.5
Average Piglets Born Alive/sow	9.2	9.2	4.3	3.2
Average Piglets Weaned/sow	7.6	7.6	3.1	2.4
Average Piglets Deaths after Being Born Alive/sow	0.015	0.034	0.37	0.84
Average Piglets Euthanized/sow	0.31	0.22	0.69	0.50
Average Piglets Laid On/sow	1.13	0.94	1.34	1.43
Average Piglets Stillborn/sow	0.47	0.47	0.92	0.65
Average Piglets Mummified/sow	0.09	0.14	0.39	0.42
Proportion Born Alive to Total Born	0.950	0.944	0.091	0.070
Proportion Weaned to Total Alive[b]	0.84	0.87	0.135	0.144
Proportion Deaths to Total Alive[b]	0.014	0.034	0.035	0.066
Proportion Euthanized to Total Alive[b]	0.024	0.029	0.052	0.059
Proportion Laid On to Total Alive[b]	0.091	0.083	0.102	0.105
Proportion Stillborn to Total Born	0.044	0.046	0.086	0.064
Proportion Mummified to Total Born	0.006	0.010	0.024	0.031

[a] Standard Deviation
[b] Total Piglets Born Alive

e. Conclusion: PULMOTIL fed continuously to reproducing female swine at 3 times the highest labeled dose, 1200 ppm, for approximately 6 months during all aspects of the reproductive cycle, produced no adverse effects in the dam or piglets. PULMOTIL fed at labeled concentrations (up to 400 ppm) to female swine used for breeding is considered safe to the dam and piglets.

4. HUMAN SAFETY:

Microbial Food Safety

The Agency used a qualitative risk assessment to evaluate available microbial food safety information regarding the proposed change in the labeling of tilmicosin phosphate (PULMOTIL 90) to allow for use in pregnant swine (sows). This risk assessment involved characterizing the hazard associated with the antimicrobial new animal drug under the proposed conditions of use. The hazard is defined as human illness, caused by antimicrobial-resistant bacteria, attributable to an animal-derived food commodity (pork), and treated with the human antimicrobial drug of interest (macrolide class antimicrobial drugs).

It was determined that the magnitude of the hazard associated with the use of tilmicosin phosphate (PULMOTIL 90) in pregnant swine (sows) was compatible with the proposed conditions of use. The Agency finds that the proposed change in labeling, and corresponding changes in numbers of animals treated and slaughtered for human consumption, does not constitute a significant microbial food safety hazard of a magnitude that an assessment of microbial food safety is warranted at this time.

No other new human food safety data were required for this supplement to NADA 141-064 (Original approval dated December 27, 1996) and this supplement did not require review of the original human food safety data. There is a 7-day withdrawal period for swine fed with tilmicosin prior to slaughter.

5. AGENCY CONCLUSIONS:

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that PULMOTIL 90 (tilmicosin phosphate) when administered in the feed at 181 to 363 g per ton, as the sole ration for a 21-day period for the control of swine respiratory disease is safe for breeding female swine during all phases of the reproductive cycle.

Federal (USA) law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this Veterinary Feed Directive (VFD) drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice.

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 use of the product in breeding females at all stages of reproduction for the control of swine respiratory disease.

In accordance with 21 CFR 514.106(b)(2)(ix), this is a category II change which did not require reevaluation of the safety or effectiveness data in the parent application.

U.S Patent Number	Date of Expiration
4,820,695	April 11, 2006

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

PULMOTIL 90 Type A medicated article label

PULMOTIL Medicated Type B Feed label

PULMOTIL Medicated Type C Feed labe