Date of Approval: February 2, 1999

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-064

PULMOTIL® 90 Type A Medicated Article

(tilmicosin phosphate)

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

I. GENERAL INFORMATION

NADA Number: 141-064

Sponsor: Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Established Name: tilmicosin phosphate

Proprietary Name: PULMOTIL® 90

Marketing Status: 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.

Effect of Supplement:

1. The addition of the following caution statement to labeling.

   "Caution: Do not allow horses or other equine access to feeds containing tilmicosin."

2. The codification under 21 CFR 556.735, of an acceptable daily intake (ADI) in man and a muscle tolerance for parent tilmicosin in swine muscle.

II. INDICATIONS FOR USE

PULMOTIL® 90 is indicated for the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

III. DOSAGE

A. *Dosage Form*: Type A medicated article containing tilmicosin phosphate at 90.9 g/lb (200 g/kg), to be mixed either in a Type B medicated feed or in a finished Type C medicated feed for swine. PULMOTIL® 90 is supplied in 25-lb bags.

B. *Route of Administration*: Oral, in feed.

C. *Recommended Dose Range:* PULMOTIL® 90 should be fed at a dose rate of 181 g to 363 g tilmicosin phosphate per ton of complete feed (200 to 400 ppm). Feed continuously as the sole ration for a 21-day period, beginning approximately seven (7) days before an anticipated disease outbreak.

IV. EFFECTIVENESS

As discussed in the FOI Summary for the original approval of NADA 141-064.

V. ANIMAL SAFETY

As discussed in the FOI Summary for the original approval of NADA 141-064.

The safety of PULMOTIL® 90 in the equine was evaluated in a study in which tilmicosin was included in the diet of 18 adult horses for a period of 14 days at dose levels of 400, 1200, and 2000 ppm. Some horses at both the low and high dose levels demonstrated gastrointestinal disturbance, with more severe colic evident at the higher levels. One horse died after consuming the 2000 ppm diet.

Accordingly, the following caution statement has been added to labeling: Do not allow horses or other equine access to feeds containing tilmicosin.

VI. HUMAN FOOD SAFETY

A. Toxicology and residue and metabolism studies

The basic toxicology and residue chemistry studies that support the use of tilmicosin in swine are summarized in the FOI Summaries for the original approvals of tilmicosin under NADA 140-929 (toxicology data) and NADA 141-064 (residue and metabolism data). Based on the toxicology studies, an acceptable daily intake of 25 mcg/kg bw/day was calculated, and the safe concentrations for total tilmicosin residues of 5 ppm in muscle, 15 ppm in liver, 30 ppm in kidney, and 30 ppm in fat were assigned to swine. The residue and metabolism studies established 7.5 ppm as the tolerance for residues of parent tilmicosin (the marker residue) in swine liver (the target tissue).

B. Assignment of a muscle tolerance

A muscle tolerance of 0.1 ppm parent tilmicosin is assigned following a review of the residue studies conducted with tilmicosin in swine in support of the original approval of NADA 141-064. The residue and metabolism data in study T5C759201 show that unchanged tilmicosin represents greater than 50% of the total residue present in swine muscle tissue following administration of the drug in feed. Those results confirm that parent tilmicosin can serve as the marker residue in swine muscle.

The muscle tolerance value of 0.1 ppm is assigned based on the data in total residue study T5C759201 and in marker residue depletion study T5C619301. Those data show that parent tilmicosin was in the range of 0.2 to 0.4 ppm at zero withdrawal (6 to 12 hours) following treatment with tilmicosin at levels of 400 ppm in the feed. Residues of unchanged tilmicosin depleted rapidly from swine muscle and were less than the 0.02 ppm detection limit of the HPLC assay used in the residue study at 7 days of withdrawal. The choice of 0.1 ppm as the tolerance for tilmicosin in swine muscle makes it possible to identify animals that have been treated with the drug and slaughtered 2 to 3 days post-treatment.

VII. AGENCY CONCLUSIONS

The minor label revision submitted in support of this supplemental NADA complies with the requirements of Section 512 of the Food, Drug, and Cosmetic Act and Part 514 of the implementing regulations. In accordance with 21 CFR 514.106(b)(1)(xiv), this is a Category I supplement which did not require re-evaluation of the safety and effectiveness data of the parent application.

Based on data submitted in support of the original approval of this NADA, a tolerance of 0.1 ppm has been established with this supplement for tilmicosin in swine muscle. The acceptable daily intake (ADI) (25 micrograms per kilogram of body weight per day) and the tolerance for tilmicosin in swine muscle (0.1 ppm) will be codified under 21 CFR 556.735.

FDA has determined under 21 CFR 25.33(a)(1) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

PULMOTIL® 90 is under U.S. patent number 4,820,695 which expires April 11, 2006.

VIII. APPROVED PRODUCT LABELING

A copy of the draft facsimile labeling is attached to this document.

A. PULMOTIL® Type A Medicated Article Bag Label

B. PULMOTIL® Bluebird Label for Type B Medicated Feed

C. PULMOTIL® Bluebird Label for Type C Medicated Feed