

Date of Approval: NOV 15 2001

**FREEDOM OF INFORMATION SUMMARY**

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

**NADA 141-064**

**Pulmotil® 90 tilmicosin**

For Revision of the Approved Pulmotil® 90 tilmicosin Labeling 1) removal of the MIC chart; 2) additions to the Pharmacology section of the label; 3) additional CAUTION that discourages continuous use for more than 21 days and limits use of each VFD form to 90 days. Changes to the VFD are inclusion of the additional CAUTION like the label and 2) addition of a 90-day maximum for the expiration of the VFD.

**SPONSORED BY:**

**Elanco Animal Health**

**I. GENERAL INFORMATION**

NADA Number: 141-064

Sponsor: Elanco Animal Health  
Lily Corporate Center  
Indianapolis, Indiana 46285

Established Name: tilmicosin phosphate

Trade Name: Pulmotil<sup>®</sup> 90 tilmicosin

Marketing Status: Veterinary Feed Directive (VFD)

Effect of Supplement: Changes to the label are 1) removal of the MIC chart; 2) additions to the Pharmacology section of the label; 3) additional CAUTION that discourages continuous use for more than 21 days and limits use of each VFD form to 90 days. Changes to the VFD are inclusion of the additional CAUTION like the label and 2) addition of a 90-day maximum for the expiration of the VFD.

**II. INDICATIONS FOR USE**

For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

**III. DOSAGE**

A. Dosage Form:

Type A Medicated Article

B. Route of Administration:

Oral, in feed

C. Recommended Dosage:

Fed continuously at 181 to 363 grams tilmicosin per ton (200 to 400 ppm) of type C medicated feed as the sole ration for a 21-day period, beginning 7 days before an anticipated disease outbreak.

**IV. EFFECTIVENESS**

No further effectiveness data were required from the original approval dated December 27, 1996.

**V. ANIMAL SAFETY**

No further target animal safety data were required from the original approval dated December 27, 1996.

**VI. HUMAN SAFETY**

No further human food safety data were required from the original approval dated December 27, 1996.

**VII. AGENCY CONCLUSIONS**

The information submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and implementing regulations at Part 514 of Title 21, Code of Federal Regulations (21 CFR 514) for Pulmotil® 90 tilmicosin for swine, to allow for the revisions of the labeling and VFD.

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

The agency 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 human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals does not qualify for marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

**VIII. APPROVED PRODUCT LABELING**

Pulmotil® 90 tilmicosin Type A Medicated Article label

Medicated Type B and C Bluebird labels

Veterinary Feed Directive

Copies of applicable labeling may be obtained by writing to:

Freedom of Information Staff (HFI-35)  
Room 12A16  
5600 Fisher's Lane  
Rockville, MD 20857

**ELANCO**

AF0472-10K



Net Weight 10 Kg (22.7 lb)

**Type A Medicated Article**

|                        |
|------------------------|
| Do not feed undiluted. |
|------------------------|

**CAUTION:** Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive 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.

**Active Drug Ingredient:** tilmicosin (as tilmicosin phosphate) 90.7 g per lb (200 g per kg)  
**Inert ingredients:** ground corncobs

**Description:** Pulmotil is a formulation of the antibiotic tilmicosin. Tilmicosin is produced semi-synthetically and is in the macrolide class of antibiotics. Each kilogram of Type A Medicated Article contains 200 grams (0.44 lbs) of tilmicosin adsorbed onto ground corncobs.

**Indications:** For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

**Pharmacology:** Oral dosing of tilmicosin phosphate at 181 to 363 g/ton of feed results in serum tilmicosin levels, which do not correlate with efficacy. Lung concentrations of tilmicosin are significantly higher than serum. Following seven consecutive days of administering tilmicosin-medicated feeds to swine, the concentration of tilmicosin in respiratory tissues, phagocytic cells, and nasal secretions was significantly higher than that of plasma or serum. Lung levels are achieved within 2 days after beginning feeding and plateau by 4 days. Using *in-vitro* incubation techniques, the ratio of intracellular to extracellular concentrations of tilmicosin for neutrophils, monocyte-macrophages, and alveolar-macrophages were 69, 19, and 17, respectively, after four hours of incubation. Although lower levels of accumulation were observed *in-vivo*, swine alveolar macrophages have been shown *in vitro* and *in vivo* to concentrate large amounts of tilmicosin; these cells may be important for *in vivo* distribution of the drug and may serve as an important reservoir for tilmicosin in lung tissue.

**Toxicology:** The cardiovascular system is the target of toxicity in laboratory and domestic animals given tilmicosin by oral or parenteral routes. Primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotropy). Given orally, the median lethal dose is 800 mg/kg in fasted rats and 2250 mg/kg in non-fasted rats. No compound-related lesions were found at necropsy. Results of genetic toxicology studies were all negative. Results of teratology and reproduction studies in rats were all negative. The no effect level in dogs after daily oral doses for up to one year is 4 mg/kg of body weight. 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.

**Adverse Drug Reactions:** No adverse toxicological effects were observed in swine given rations containing 2000 ppm tilmicosin for 42 days and 4000 ppm for 21 days.

**Warning:** Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling Pulmotil 90 should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a material safety data sheet, call 1-800-428-4441.

 **Warning:** Feeds containing tilmicosin must be withdrawn 7 days prior to slaughter 

**CAUTION:** Do not allow horses or other equines access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes.

Feed containing tilmicosin shall not be fed to pigs for more than 21 days during each phase of production without ceasing administration for re-evaluation of antimicrobial use by a licensed veterinarian before re-initiating a further course of therapy with an appropriate antimicrobial.

VFD expiration date must not exceed 90 days from the time of issuance. Veterinary Feed Directives (VFDs) for tilmicosin phosphate shall not be refilled.

**IMPORTANT: Must be thoroughly mixed in feeds before use.**

**Mixing Directions:** Thoroughly mix Pulmotil Type A medicated article with feed to provide a Type B medicated feed containing up to 36,300 grams tilmicosin per ton or to provide a complete Type C medicated feed containing 181 to 363 g tilmicosin per ton. Do not use in any feeds containing bentonite. Bentonite in feeds may affect the efficacy of tilmicosin.

| Starting concentration of Pulmotil Type A Medicated Article | Amount of Type A Medicated Article to add per ton | Resulting concentration in Type B Medicated Feed |                 |
|---|---|--|-----------------|
|   |   | grams per ton                                    | grams per pound |
| grams per pound   | pounds  |  |                 |
| 90.7  | 400   | 36,300   | 18.1            |
|   | 300   | 27,200   | 13.6            |
|   | 200   | 18,100   | 9.05            |

| Starting concentration of Pulmotil Type A Medicated Article | Amount of Type A Medicated Article to add per ton | Resulting concentration in Type C Medicated Feed |
|---|---|--|
|   |   | grams per ton                                    |
| grams per pound   | pounds  |  |
| 90.7  | 4   | 363  |
|   | 3   | 272  |
|   | 2   | 181  |

**Feeding Directions:** Tilmicosin is to be fed continuously at 181 grams to 363 grams per ton (200 ppm 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.

Avoid moisture and excessive heat (40° C)  
 Not to be used after the date printed on the bag.  
 NADA 141 - 064, Approved by FDA.



Eli Lilly and Company Limited, Speke Operations, Fleming Road, Liverpool L24 9LN U.K.  
 For Technical Service Call: 1-800-428-4441

Elanco®, Pulmotil®, and the diagonal color bar are registered trademarks of Eli Lilly and Company.

(Lot number and expiry date are printed on the bag.)

(8-13-2001D)

**BLUEBIRD FEED COMPANY**  
**BLUEBIRD SWINE FEED CONCENTRATE**

**Medicated Type B Feed**

**FOR USE IN SWINE FEEDS ONLY**

**Do Not Feed Undiluted**

**CAUTION:** Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive 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.

**INDICATIONS:** For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

**ACTIVE DRUG INGREDIENT:** tilmicosin (as tilmicosin phosphate) .... \_\_\_\_\_ grams per ton  
(up to 36,300 grams per ton)

**GUARANTEED ANALYSIS**

Need to list guarantees for swine outlined in AAFCO Official Publication

**INGREDIENTS**

Each ingredient must be named in accordance with the names and definitions adopted by AAFCO.

**IMPORTANT:** Must be thoroughly mixed into feeds before use.

**MIXING DIRECTIONS:** Thoroughly mix BLUEBIRD SWINE FEED CONCENTRATE with feed to provide a Type B medicated feed containing up to 36,300 grams tilmicosin per ton or to provide a complete Type C medicated feed containing 181 to 363 g tilmicosin per ton. Do not use in any feeds containing bentonite. Bentonite in feeds may affect the efficacy of tilmicosin.

| Starting concentration of BLUEBIRD Type B Medicated Feed |                 | Amount of Type B Medicated Feed to add per ton<br>pounds | Resulting concentration in Type B Medicated Feed |                 |
|--|-----------------|--|--|-----------------|
| grams per ton  | grams per pound |  | grams per ton                                    | grams per pound |
| 36,300   | 18.1            | 1,500  | 27,200   | 13.6            |
|  |                 | 1,000  | 18,100   | 9.05            |
| 27,200   | 13.6            | 1,330  | 18,100   | 9.05            |

| Starting concentration of BLUEBIRD Type B Medicated Feed |                 | Amount of Type B Medicated Feed to add per ton | Resulting concentration in Type C Medicated Feed |
|--|-----------------|--|--|
| grams per ton  | grams per pound | pounds   | grams per ton                                    |
| 36,300   | 18.1            | 20   | 363  |
|  |                 | 15   | 272  |
|  |                 | 10   | 181  |
| 27,200   | 13.6            | 26.7   | 363  |
|  |                 | 20   | 272  |
|  |                 | 13.3   | 181  |
| 18,100   | 9.05            | 40.1   | 363  |
|  |                 | 30.1   | 272  |
|  |                 | 20   | 181  |

**FEEDING DIRECTIONS:** Feed continuously as the sole ration for a 21-day period, beginning approximately seven (7) days before an expected disease outbreak.

**CAUTION:** Feed containing tilmicosin shall not be fed to pigs for more than 21 days during each phase of production without ceasing administration for re-evaluation of antimicrobial use by a licensed veterinarian before re-initiating a further course of therapy with an appropriate antimicrobial. VFD expiration date must not exceed 90 days from the time of issuance. VFDs for tilmicosin phosphate shall not be refilled.

Do not allow horses or other equines access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes.



**Warning:** Feeds containing tilmicosin must be withdrawn 7 days prior to slaughter



**Warning:** Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling Pulmotil should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a material safety data sheet, call 1-800-428-4441.

Lot no. \_\_\_\_\_

Bluebird Feed Company  
Robin, IL



Net Weight: \_\_\_\_\_ lb (\_\_\_\_\_ kg)

For emergency medical information, to report an adverse effect, or for technical service call: 1-800-428-4441  
Elanco®, Pulmotil®, and the diagonal color bar are registered trademarks of Eli Lilly and Company.  
(8-13-01D)

**BLUEBIRD FEED COMPANY****BLUEBIRD SWINE FEED****Medicated Type C Feed****FOR USE IN SWINE ONLY**

**CAUTION:** Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive 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.

**ACTIVE DRUG INGREDIENT:** Tilmicosin (as tilmicosin phosphate) .... single dose within the range of 181 to 363 g per ton

**INDICATIONS:** For the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*

**GUARANTEED ANALYSIS**

Insert list of ingredients for swine according to AAFCO Official publication

**INGREDIENTS**

Each ingredient must be named in accordance with the names and definitions adopted by AAFCO.

**FEEDING DIRECTIONS:** Feed continuously as the sole ration for a 21-day period, beginning approximately seven (7) days before an expected disease outbreak.

**CAUTION:** Feed containing tilmicosin shall not be fed to pigs for more than 21 days during each phase of production without ceasing administration for re-evaluation of antimicrobial use by a licensed veterinarian before re-initiating a further course of therapy with an appropriate antimicrobial. VFD expiration date must not exceed 90 days from the time of issuance. VFDs for tilmicosin phosphate shall not be refilled.

Do not allow horses or other equines access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes



**Warning:** Feeds containing tilmicosin must be withdrawn 7 days prior to slaughter



Lot no. \_\_\_\_\_

Bluebird Feed Company  
Robin, IL



**Net Weight:** \_\_\_\_ lb ( \_\_\_\_ kg)

For emergency medical information, to report an adverse effect, or for technical service call: 1-800-428-4441  
Elanco®, Pulmotil®, and the diagonal color bar are registered trademarks of Eli Lilly and Company.  
(6-25-01D)

**PULMOTIL® (tilmicosin) Veterinary Feed Directive**

|               |                    |
|---------------|--------------------|
| Client _____  | Veterinarian _____ |
| Address _____ | Address _____      |
| _____         | _____              |
| _____         | _____              |
| Phone _____   | _____              |
| Fax:# _____   | Fax # _____        |

Swine to be treated (number and location): \_\_\_\_\_

Mix into Type C Medicated Feed to provide:                      **181 g/ton**                      **272 g/ton**                      **363 g/ton**

                                          

**Warning:** Feeds containing tilmicosin must be withdrawn 7 days prior to slaughter.

**Feeding Directions:** Feed continuously as the sole ration for 21 days beginning approximately 7 days before an expected outbreak of swine respiratory disease.

**Special Instructions:** \_\_\_\_\_

Expiration Date: \_\_\_\_\_ Amount of final (Type C) feed \_\_\_\_\_  
Month/Day/Year (Not to exceed 90 days)

Veterinarian's Signature: \_\_\_\_\_ Date: \_\_\_\_\_

License Number and State: \_\_\_\_\_

\*\*\*\*\*  
**CAUTION:** Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed bearing or containing this veterinary feed directive drug shall be fed to animals only by or under a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice. Extra-label use, (i.e., use of this VFD feed in a manner other than as provided for in the VFD drug approval) is strictly prohibited.  
**Indications:** Pulmotil is indicated for the control of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasturella multocida*.  
**CAUTION:** Feed containing tilmicosin shall not be fed to pigs for more than 21 days during each phase of production without ceasing administration for re-evaluation of antimicrobial use by a licensed veterinarian before re-initiating a further course of therapy with an appropriate antimicrobial. VFD expiration date must not exceed 90 days from the time of issuance. VFDs for tilmicosin shall not be refilled.  
 Do not allow horses or other equines access to feeds containing tilmicosin. The safety of tilmicosin has not been established in pregnant swine or swine intended for breeding purposes.

**Mixing Directions:** Thoroughly mix Pulmotil Type A medicated article or Type B medicated feed to provide a complete Type C medicated feed containing 181 to 363 g tilmicosin per ton. Do not use in any feeds containing bentonite. Bentonite in feeds may affect the efficacy of tilmicosin.

| Starting concentration of Pulmotil Type A Medicated Article<br>grams per pound | Amount Type A Medicated Article to add<br>per ton<br>pounds | Resulting concentration in Type C Medicated Feed<br>grams per ton |
|--|---|---|
| 90.7   | 4   | 363   |
|  | 3   | 272   |
|  | 2   | 181   |
| Starting concentration of Pulmotil Type B Medicated Article<br>grams per pound | Amount Type B Medicated Feed to add<br>per ton<br>pounds    | Resulting concentration in Type C Medicated Feed<br>grams per ton |
| 18.1   | 20  | 363   |
|  | 15  | 272   |
|  | 10  | 181   |

**Warning:** Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling Pulmotil should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a material safety data sheet, call 1-800-428-4441.

**For Technical Service Call: 1-800-428-4441**  
 Avoid moisture and excessive heat (40° C)  
 NADA 141 - 064, Approved by FDA.  
 PULMOTIL® is a registered trademark of Eli Lilly and Company

Elanco Animal Health  
 A Division of Eli Lilly and Company  
 Indianapolis, IN 46285, USA



(6-25-2001D)

White Copy - Supplier                      Canary Copy - Client                      Pink Copy - Veterinarian