Label **Use/Dose**

ELANCO ANIMAL HEALTH
A Division of Eli Lilly & Co.
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PULMOTIL® AC

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Elanco

tilmicosin phosphate

(250 mg/ml tilmicosin)

Aqueous concentrate for oral use in drinking water.

For swine only.

Macrolide Antibiotic.

Do not inject this product. Injection of tilmicosin has been shown to be fatal in swine and non-human primates, and may be fatal in horses and goats.

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.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Active Drug Ingredient: tilmicosin (as tilmicosin phosphate) 250 mg/ml

Description: Pulmotil is a formulation of the antibiotic tilmicosin. Tilmicosin is produced semi-synthetically and is in the macrolide class of antibiotics. Each milliliter (mL) of Pulmotil aqueous concentrate solution contains 250 mg of tilmicosin.

Indications: 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.

Dosage and Administration: Must be diluted before administration to animals. Include in the drinking water to provide a concentration of 200 mg tilmicosin per liter (200 ppm). One 960 ml bottle is sufficient to medicate 1200 liters (320 gallons) of drinking water for pigs. The medicated water should be administered for (5) five consecutive days.

Use within 24 hours of mixing with water. Do not use rusty containers for medicated water as they may affect product integrity.

When using a water medicating pump with a 1:128 inclusion rate, add 1 bottle (960 ml) of Pulmotil AC per 2.5 gallons of stock solution.

WARNINGS:

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.

RESIDUE WARNING: Swine intended for human consumption must not be slaughtered within 7 days of the last treatment with this product.

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. β-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.

Precautions:

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

Always treat the fewest number of animals necessary to control a respiratory disease outbreak. Prescriptions shall not be refilled. Concurrent use of Pulmotil AC and another macrolide by any route is not advised. Use of another macrolide immediately following this use of Pulmotil AC is not advised.

Adverse Reactions in Animals: Decreased water consumption was observed in healthy pigs administered tilmicosin in target animal safety studies. Ensure that pigs have continuous access to medicated water during the treatment period. Monitor pigs for signs of water refusal and dehydration while being treated. If decreased water consumption occurs, replace the medicated drinking water with fresh non-medicated water and contact your veterinarian.

Clinical Pharmacology: Tilmicosin is a macrolide antibiotic with *in vitro* antibacterial activity primarily against Gram-positive bacteria, although certain Gram-negative bacteria are also susceptible. Macrolides interfere with bacterial protein synthesis by reversibly binding to the 50S subunit of the ribosome. They are typically regarded as being bacteriostatic, but at high concentrations can be bactericidal. When administered orally to pigs via the drinking water, tilmicosin is rapidly absorbed and slowly eliminated from the body. Tilmicosin distributes rapidly to the target tissues. Detectable levels are found in lung tissue as early as 6 hours and peak at about 5 days after the commencement of treatment. The relationship of serum tilmicosin concentration to lung tilmicosin concentration or the concentrations in bronchial secretion has not been determined. In addition, the extent to which total lung concentrations represent free (active) drug has not been defined. Therefore, no conclusions can be made with regard to the clinical relevance of elevated tilmicosin concentrations in the lung. Tilmicosin has been shown to concentrate within alveolar macrophages. It is also found at fairly high concentrations in liver and kidney tissue, as it is excreted both via the bile into the feces and also via the urine.

Effectiveness: The effectiveness of Pulmotil AC for the control of SRD associated with *P. multocida* and *H. parasuis* was confirmed in a natural infection field study across six U.S. sites. A total of 960 commercial-type grower pigs were enrolled and assigned to the tilmicosin-treated group (200 mg tilmicosin/L in drinking water for 5 consecutive days), or a non-medicated control group. Pigs that 1) were found dead and were diagnosed with SRD, or 2) had a depression score 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. At each site, treatments were initiated when at least 15% of the pigs were classified as clinically affected. After the 5-day treatment period and a 4-day post-treatment period, pigs were evaluated for treatment success (respiration and depression scores of 1 or 0 and rectal temperature < 104.5 °F), and were euthanized and evaluated for lung lesions. A significantly higher (p = 0.0118) success rate (based on back-transformed least squares means) was detected for the tilmicosin.treated group (275/473, 58.64%) compared to the control group (230/475, 47.89%).

The effectiveness of Pulmotil AC for the control of SRD associated with *M. hyopneumoniae* in the presence of PRRSV was confirmed in an induced infection model study. A total of 340 commercial-type pigs were enrolled and challenged with *M. hyopneumoniae* (single infection) or *M. hyopneumoniae* and PRRSV (co-infection). When necropsied sentinel pigs had at least 5% lung lesion involvement, study pigs were treated with Pulmotil AC (200 mg tilmicosin/L in drinking water) or non-medicated water for 5 consecutive days. After the 5-day treatment period and a 4 day post-treatment period, pigs were euthanized and evaluated for lung lesions.

For both the single infection and co-infection groups, the lung lesion percentage was statistically significantly different (p = 0.005 and p = 0.0004, respectively) in favor of the tilmicosin phosphate-treated group (21.01% and 31.74%, respectively) compared with the control group (28.26% and 43.04%, respectively).

Animal Safety: A pharmacokinetic study was conducted to evaluate Pulmotil AC concentrate solution in pigs. The results were compared to pharmacokinetic data generated with Pulmotil 90 Type A medicated article (NADA 141-064). The data demonstrates that blood and tissue levels of tilmicosin when administered to pigs at 200 mg/L (ppm) in water were consistently lower than when tilmicosin was administered to pigs at 181 g/ton (200 ppm) in feed.

A target animal safety study was conducted to evaluate the tolerance of Pulmotil AC concentrate solution in pigs when administered in drinking water. Twenty pigs were administered medicated water at 0, 200, 400, or 600 mg/L (0, 1X, 2X, or 3X the labeled dose) for 5 consecutive days or 200 mg/L for 10 consecutive days. No treatment-related lesions were observed in any animals at necropsy. Water consumption was decreased in all tilmicosin-treated groups compared to the non-medicated group. One pig in the 600 mg/L group was euthanized due to decreased water consumption, neurological signs attributed to severe dehydration, and subsequent refusal to drink non-medicated water. Two pigs in the 400 mg/L group had reduced water intake and displayed mild clinical signs attributed to dehydration. One pig recovered after being offered non-medicated water. The second pig completed the treatment regimen without intervention.

Hydration and water consumption were evaluated during the control of SRD effectiveness field study. Tilmicosin was administered to study pigs in drinking water at 200 mg/l for 5 consecutive days. There was no statistically significant difference in water consumption between tilmicosin-treated pigs and pigs receiving non-medicated water. A subset of study pigs (20 tilmicosin-treated pigs and 20 non-medicated pigs) were evaluated for hydration via a physical examination and analysis of blood samples for hematocrit, total protein, creatinine, and blood urea nitrogen. There were no abnormal physical examination findings or clinically relevant differences in clinical pathology variables between tilmicosin.treated pigs and pigs receiving non-medicated water.

How Supplied: Pulmotil AC is provided in a 960 ml amber-colored plastic bottle sealed with a plastic screw cap.

Storage Conditions:

Store at or below 86° F (30° C). Protect from direct sunlight.

Restricted Drug (California) - Use Only as Directed

NADA # 141-361, Approved by FDA

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

960 ml	AH0470	YL089279AMX

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