Pulmotil® AC
(tilmicosin phosphate)

aqueous concentrate formulation

The newest member of your team to help control swine respiratory disease

FULL VALUE PIGS™

Elanco
Pulmotil® AC
Tilmicosin Phosphate™

www.elanco.us

Pulmotil AC
(tilmicosin phosphate)

Combining the benefits of a liquid with the strength of Pulmotil

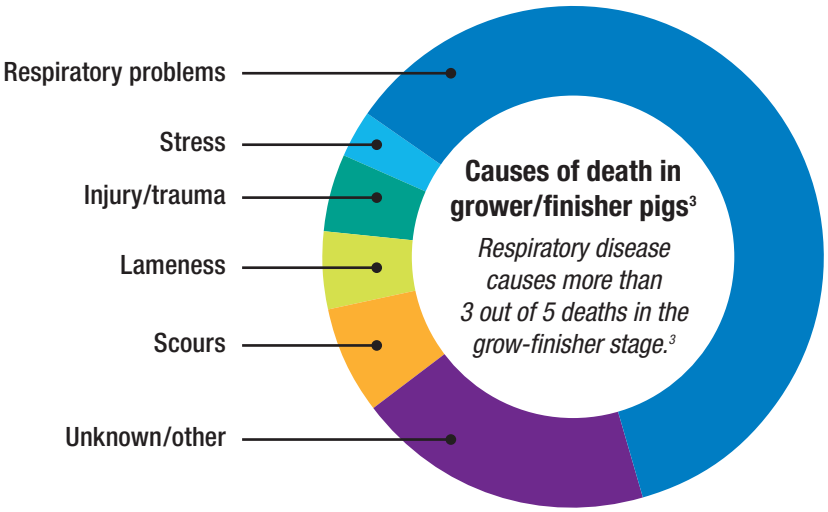
Pulmotil AC is an aqueous concentrate formulation for the control of swine respiratory disease associated with *Pasteurella multocida* and *Haemophilus parasuis* in groups of swine in buildings where a respiratory disease outbreak is diagnosed.

RESPIRATORY DISEASE: Prevalence

- Prevalent in all swine-producing areas[1]
- A serious disease problem in modern swine production[1]
- Often seasonal in nature, peaking in periods of environmental stress[1]

RESPIRATORY DISEASE: Impact

- An economically important disease[2]
- The No. 1 cause of grow-finish mortality[3]
- Pigs grow slower, are less efficient and less likely to become *Full Value Pigs*™ [4]



Winter and other environmentally stressful periods often correspond to an increase in respiratory disease in herds.[1]

RESPIRATORY DISEASE: Cost

- Pneumonia has been estimated to cost up to $5.84 per pig[5]

IMPORTANT SAFETY INFORMATION

See label on page 4 for complete safety and use information, including boxed human warning.

Pulmotil AC is to be used by, or on the order of, a licensed veterinarian. Not for injection. For use only in swine. Swine intended for human consumption must not be slaughtered within 7 days of treatment. 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. The safety of tilmicosin has not been established in male swine intended for breeding purposes. Concurrent use of Pulmotil AC and another macrolide by any route, or use of another macrolide immediately following this use of Pulmotil AC, is not advised.

Pulmotil® AC: Go with the flow

New Pulmotil AC makes it easy to go with the flow. With a targeted respiratory disease spectrum and a unique mode of action, Pulmotil AC rapidly delivers the active ingredient to the site of infection. And Pulmotil AC works with the pig's immune system, rapidly accumulating in swine phagocytes.[6] The aqueous concentration makes respiratory disease control:

Easy

- Water medication for easy mixing
- No need to inject each animal
- Start & stop at your convenience

Fast

- No waiting for feed bins to empty
- No need to formulate new rations
- After 24 hours, active substance detectable in:[6]
  - Lung tissue
  - Alveolar macrophages
  - Bronchial epithelium

Cost-effective

- Eliminate labor costs associated with injectable treatments*

Effective

- Controls key respiratory disease pathogens (*Haemophilus parasuis* & *Pasteurella multocida*)
- Unique mode of action works with pigs' immune systems to deliver active ingredient to infection site[7]

A key component of *Full Value Pigs*™

Pulmotil AC can help improve swine health, leading to *Full Value Pigs*:

- **Health:** Incorporating diagnostic testing, biosecurity, attrition and products into disease management and herd health
- **Feed:** Getting the best results from producers' biggest input
- **Output:** Using revenue and variation to calculate the right weight at the right time
- **Access:** Assurance that producers will be able to provide quality pork to their market of choice

Study outcomes[8]

About the study

The trial was conducted using a complete, random block design. The trial included six sites within the United States, with 160 pigs at each site for a total of 960 pigs.[8] When at least 15% of the candidate group were classified as clinically affected, pigs were allocated to pens and treatment group.[8]

Variable	Pulmotil AC	Control	Difference	P-value
Treatment success rate[8,**] (day 9)	58.6%	47.9%	10.7%	0.0118
Average daily gain[8,†] (0-9 days)	1.04 lbs.	0.79 lbs.	+0.25 lbs.	<0.0001

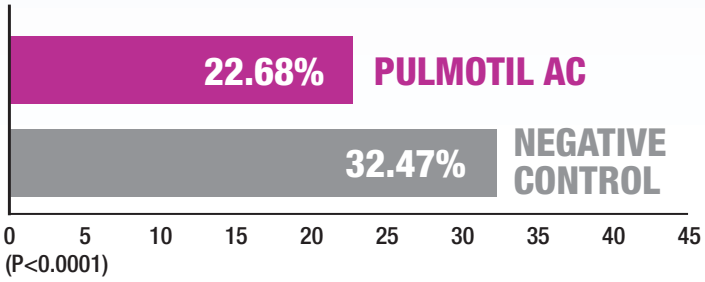
In a trial, pigs treated with Pulmotil AC demonstrated a better success rate compared to control pigs.[8]

* Assumption: Labor costs with injectable treatments typically include one or two people at $20/hour.

** Each pig classified as treatment success or failure on last day of study (day 9). Treatment success defined as a pig with rectal temperature of <104.5° F, **and** a respiratory score equal to 1 or 0 **and** a depression score equal to 1 or 0. All end-of-study pigs not meeting treatment success criteria were classified as treatment failures.

† Improvement in average daily gain achieved as a result of control of swine respiratory disease associated with *Pasteurella multocida* and *Haemophilus parasuis*.

Severe lung lesion scores[9]



Severe lung lesion scores were about 10 percentage points lower for pigs treated with Pulmotil AC compared to those in a negative control group.[9]

[1] Sorensen, V., Jorsal, S. and Mousing, J. 2006. "Diseases of the Respiratory System." Diseases of Swine 9th ed.: 149, 154, 158.

[2] Holtkamp, D., Rotto, H. and Garcia, R. 2007. "Economic Cost of Major Health Challenges in Large US Swine Production Systems." Proc. AASV. 8: 5-90.

[3] USDA APHIS. October 2007. "Swine 2006 Part I: Reference of Swine Health and Management in the United States, 2006." National Animal Health Monitoring System. Accessed 3/11/2013. Available at: <http://www.aphis.usda.gov/animal_health/nahms/swine/downloads/swine2006/Swine2006_dr_PartI.pdf>.

[4] Tubbs, R. and Deen, J. 1997. "Economics of Respiratory and Enteric Diseases." Amer. Assoc. Swine Prac.:361-364.

[5] Miller, G. and Dorn, C. 1990. "Costs of Swine Diseases to Producers in Ohio." Preventive Vet. Med. 8: 183-190.

[6] Elanco. 2002. "Pulmotil® AC Tilmicosin Aqueous Concentrate Drinking Water Medication for Swine." International Registration Summary Dossier. 1-116. Data on file.

[7] Blais, J. and Chamberland, S. 1994. "Intracellular Accumulation of Tilmicosin in Primary Swine Alveolar Macrophages." Proc. 13th IPVS Cong.: 331.

[8] Van Koevering, M., and Friesen, K. July 2012. "Clinical Study: An Efficacy Study with Pulmotil® AC for the Control of Naturally Occurring Swine Respiratory Disease." Study T5CAM0709. Elanco Animal Health. Data on file.

[9] Elanco study T5CAM0709. Lung Lesion Data (Supplemental Data). Data on file.

Pulmotil® AC

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.

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.

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. 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.

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 commercialtype 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%).

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, IX, 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