

MICOTIL[®] (tilmicosin injection) AND THE CATTLE IMMUNE SYSTEM — WORKING TOGETHER



Micotil is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*, and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*.

Important Safety Information

Before using this product, it is important to read the entire product insert, including the boxed human warning. Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Not for human use. Injection of this drug in humans has been associated with fatalities. Keep out of reach of children. Do not use in automatically powered syringes. Exercise extreme caution to avoid accidental self-injection. In case of human injection, consult a physician immediately and apply ice or cold pack to injection site while avoiding direct contact with the skin. Avoid contact with eyes. Always use proper drug handling procedures to avoid accidental self-injection. Consult your veterinarian on the safe handling and use of all injectable products prior to administration. For use in cattle or sheep only. Inject subcutaneously. Injection of this antibiotic has been shown to be fatal in swine and non-human primates, and may be fatal in horses and goats. Do not use in lambs less than 15 kg body weight. Do not use in female dairy cattle 20 months of age or older. Use in lactating dairy cattle or sheep may cause milk residues. The following adverse reactions have been reported: in cattle: injection site swelling and inflammation, lameness, collapse, anaphylaxis/anaphylactoid reactions, decreased food and water consumption, and death; in sheep: dyspnea and death. Micotil has a pre-slaughter withdrawal time of 42 days.

Elanco

Micotil[®]
Tilmicosin Injection

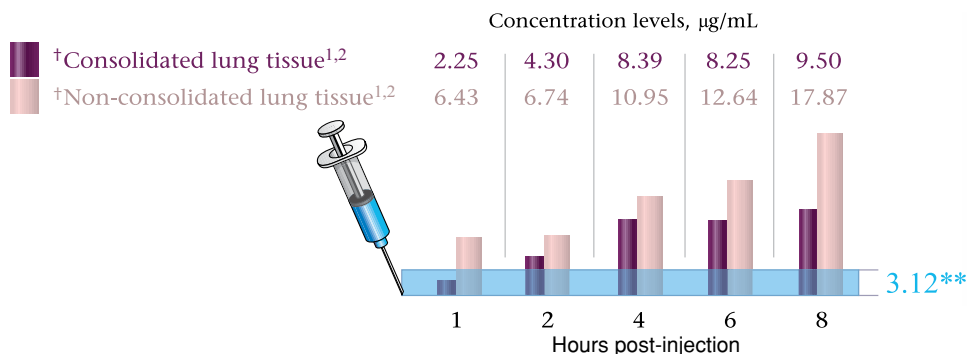
Still the One

Elanco

Micotil is the proven, long-lasting Bovine Respiratory Disease (BRD) treatment that offers a flexible, cost-effective dose range for both metaphylaxis and individual pull-and-treat therapy.

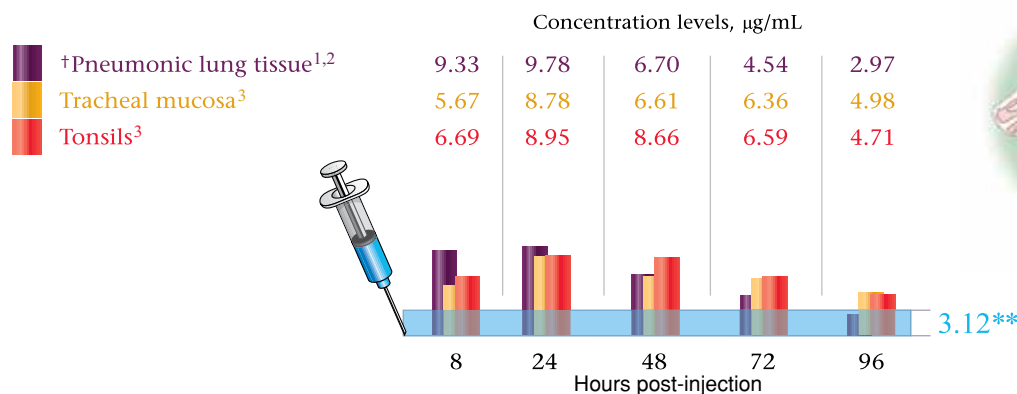
In the lungs in one hour*

- Micotil reaches cattle's lungs in one hour.^{1,2}
- Micotil reaches consolidated lungs in two hours.^{1,2}



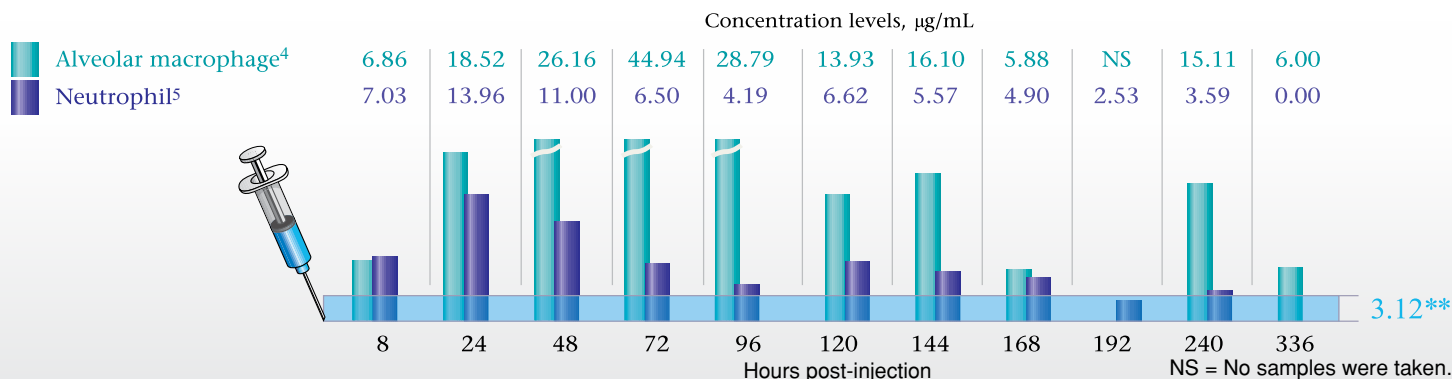
Throughout the respiratory tract for three to four days*

- Micotil maintains three to four days of effective concentration levels throughout the respiratory tract, including the pneumonic lung tissue,^{1,2} tracheal mucosa³ and tonsils³ — where the respiratory infectious process begins.



In the immune cells for up to 10 days*

- Micotil maintains levels in alveolar macrophages³ and neutrophils⁴ for up to 10 days.
- These immune cells deliver Micotil to the site of the infection where and when it's needed most.



*The clinical significance of this data has not been demonstrated. Data based on 10 mg/kg of body weight (1.5 mL per 100 lbs) dosage level.

**Ninety-five percent of the *Mannheimia (Pasteurella) haemolytica* isolates were inhibited by 3.12 µg/mL.

†Lung tissue from cattle with acute pneumonia.



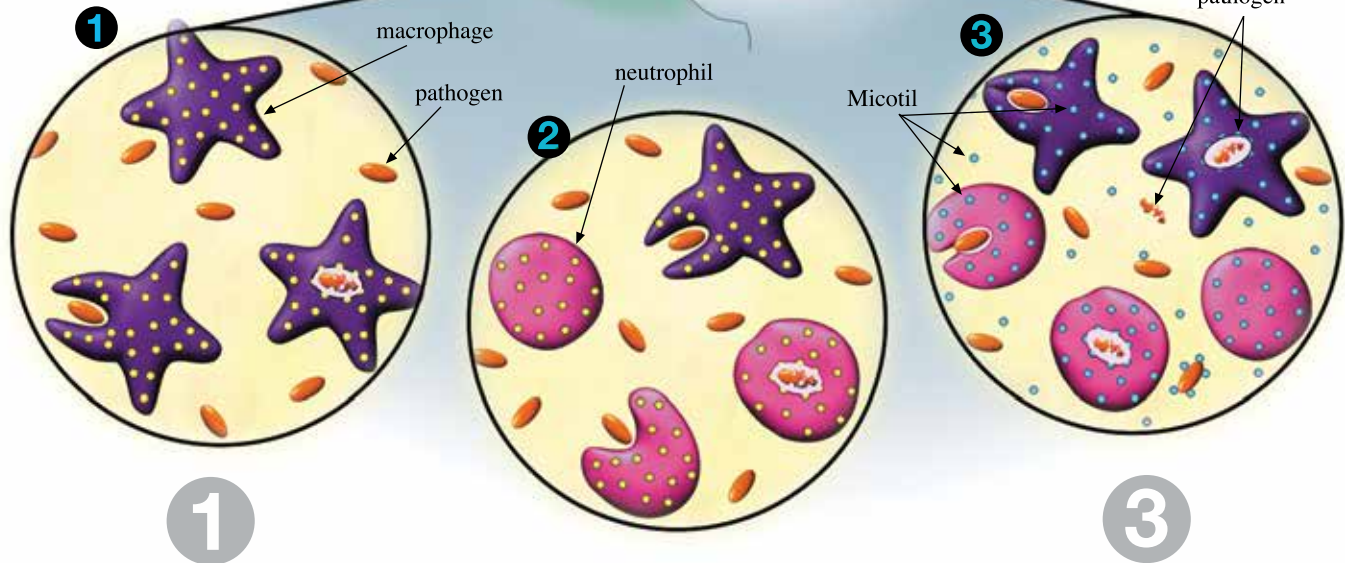
Reaches cattle's lungs fast*^{1,2}



Long-lasting levels*^{3,5}

Micotil and the immune response system — working together

Animal's immune system responds to bacterial infections.



1

Alveolar macrophages in the lungs are the first line of defense for BRD. They engulf pathogens, kill and digest them.

2

Neutrophils are the second line of defense, moving from the blood stream to the site of infection. Like macrophages, they also kill bacteria by engulfing and digesting them.

3

Micotil concentrates in the alveolar macrophages and neutrophils and is carried straight to the site of BRD infection where it is needed most.

*The clinical significance of this data has not been demonstrated.

See label on back for complete use information, including boxed human warnings and non-target species safety information.



Micotil® (tilmicosin injection) — A tried-and-true market- share leader you depend on

In today's marketplace you have choices, so which bovine respiratory disease (BRD) product will you trust? By providing dependable results in more than 100 million head of cattle, Micotil has earned your confidence as a flexible BRD solution that reduces deaths (mortality) and pulls (morbidity) in your operation.⁵ Micotil is approved for the treatment and control of BRD. You can trust Micotil to deliver bottom-line value and results.

The BRD product you continue to turn to is still the one you trust today because Micotil offers:

- **A PROVEN TRACK RECORD** — 35 trials⁶ on 22,640 head demonstrate Micotil's proven efficacy in controlling respiratory disease on arrival
- **DEPENDABLE RESULTS** — Micotil has consistently delivered results in millions of cattle
- **FEWER LATE PULLS** — Research shows that compared to Excede, Micotil-treated cattle have fewer late pulls^{7,8}
- **BOTTOM-LINE VALUE** — Based on current premium antibiotic market prices,⁹ Micotil delivers the best-in-class value
- **FLEX DOSE** — Micotil is the only antibiotic to offer a flexible dose range for BRD metaphylaxis, allowing you to better manage on-arrival weight and risk variation^{10,11}

¹Thompson, T., Laudert, S. et al. 1994. Micotil: pharmacokinetics of tilmicosin, a semi-synthetic macrolide antibiotic, in acutely pneumonic cattle and primary bovine alveolar macrophages. 6th European Assoc Vet Pharmacology and Therapeutics Congress, Aug., 31-32.
²Thompson, T. and Lawrence, K. 1994. Micotil: pharmacokinetics of tilmicosin, a semi-synthetic macrolide antibiotic, in cattle. 6th European Assoc Vet Pharmacology and Therapeutics Congress, Aug., 55-56.
³Fossler, S., Moran, J. et al. 1998. Pharmacologic Mechanism for Tilmicosin in the Control of Cattle Pneumonia. Proceedings of the 79th Annual Meeting of the Conference of Research Workers in Animal Diseases. 82.
⁴Elanco Animal Health. Data on file.
⁵Fossler, S., Moran, J. et al. 2000. Distribution of Tilmicosin into Bovine Peripheral Neutrophils Following Micotil Treatment. Proceedings of the 81st Annual Meeting of the Conference of Research Workers in Animal Diseases. 101.
⁶McClary, D., Carter, B. et al. 2013. The Use of Micotil® (tilmicosin injection) Metaphylaxis for the Control of Bovine Respiratory Disease (BRD): A 35-study Summary. Elanco data on file.
⁷Independent Study No. PreCon Mys.E. 2012.
⁸Hibbard, B., Meeuwse, D. et al. 2004. Excede vs. Micotil for control of bovine respiratory disease using a postmetaphylaxis interval.
⁹Elanco Animal Health. Data on file.
¹⁰Elanco Animal Health. Data on file.
¹¹Elanco Animal Health. Data on file.



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NADA 140-929, Approved by FDA

Micotil® 300 Injection*

Tilmicosin Injection, USP

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: Micotil® is a solution of the antibiotic tilmicosin. Each mL contains 300 mg of tilmicosin, USP as tilmicosin phosphate in 25% propylene glycol, phosphoric acid as needed to adjust pH and water for injection, Q.S. Tilmicosin, USP is produced semi-synthetically and is in the macrolide class of antibiotics.

Indications: Micotil is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* and for the treatment of ovine respiratory disease (ORD) associated with *Mannheimia haemolytica*. Micotil is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*.

Dosage and Administration: Inject Subcutaneously in Cattle and Sheep Only. In cattle, administer a single subcutaneous dose of 10 to 20 mg/kg of body weight (1 to 2 mL/30 kg or 1.5 to 3 mL per 100 lbs). In sheep greater than 15 kg, administer a single subcutaneous dose of 10 mg/kg of body weight (1 mL/30 kg or 1.5 mL per 100 lbs). Do not inject more than 10 mL per injection site.

If no improvement is noted within 48-hours, the diagnosis should be reevaluated.

For cattle and sheep, injection under the skin in the neck is suggested. If not accessible, inject under the skin behind the shoulders and over the ribs.

Note: Swelling at the subcutaneous site of injection may be observed.

Contraindications: Do not use in automatically powered syringes. Do not administer intravenously to cattle or sheep.

Intravenous injection in cattle or sheep will be fatal. Do not use in lambs less than 15 kg body weight. Do not administer to animals other than cattle or sheep. Injection of this antibiotic has been shown to be fatal in swine and non-human primates, and it may be fatal in horses and goats.

Warnings:

Human Warnings: Not for human use. Injection of this drug in humans has been associated with fatalities. Keep out of reach of children. Do not use in automatically powered syringes. Exercise extreme caution to avoid accidental self-injection. In case of human injection, consult a physician immediately and apply ice or cold pack to injection site while avoiding direct contact with the skin. Emergency medical telephone numbers are 1-800-722-0987 or 1-800-428-4441. Avoid contact with eyes.

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 Micotil-induced tachycardia and negative inotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. β -adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs. Epinephrine potentiated lethality of Micotil in pigs. This antibiotic persists in tissues for several days.

Advertencias Para El Ser Humano: Este producto no es para uso humano. La inyección de este medicamento al ser humano se ha asociado con muertes. Mantenga fuera del alcance de los niños. No use en jeringas operadas automáticamente. Proceda con extrema cautela para evitar la autoinyección accidental. En caso de inyección a un ser humano, consulte a un médico inmediatamente y aplique hielo o una bolsa de hielo sobre el sitio de la inyección, evitando el contacto directo con la piel. Los números de teléfono para emergencias médicas son 1-800-722-0987 ó 1-800-428-4441. Evite el contacto con los ojos.

Nota Para El Médico: El sistema cardiovascular es el blanco de la toxicidad y debe vigilarse estrechamente. La toxicidad cardiovascular puede deberse al bloqueo de los canales de calcio. En los perros, la administración intravenosa de calcio compensó la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensó parcialmente los efectos inotrópicos negativos inducidos por Micotil en perros. Los antagonistas β -adrenérgicos, como propranolol, exacerbaron el inotropismo negativo de Micotil en los perros. La epinefrina potenció la letalidad de Micotil en cerdos. Este antibiótico persiste en los tejidos por varios días.

Residue Warnings: Animals intended for human consumption must not be slaughtered within 42 days of the last treatment. Not for use in lactating dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Not for use in lactating ewes producing milk for human consumption.

For Subcutaneous Use in Cattle and Sheep Only. Do Not Use in Automatically Powered Syringes. Solo Para Uso Subcutáneo en Bovinos y Ovinos. No Administrar con Jeringas Accionadas Automáticamente.

Precautions: Read accompanying literature fully before use. Intramuscular injection will cause a local reaction which may result in trim loss of edible tissue at slaughter. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined.

Adverse Reactions: The following adverse reactions have been reported post-approval: In cattle: injection site swelling and inflammation, lameness, collapse, anaphylaxis/anaphylactoid reactions, decreased food and water consumption, and death. In sheep: dyspnea and death. For a complete listing of adverse reactions for tilmicosin phosphate reported to the CVM see <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm>

Clinical Pharmacology: A single subcutaneous injection of Micotil at 10 mg/kg of body weight dose in cattle resulted in peak tilmicosin levels within one hour and detectable levels (0.07 µg/mL) in serum beyond 3 days. However, lung concentrations of tilmicosin remained above the tilmicosin MIC 95% of 3.12 µg/mL for *Mannheimia haemolytica* for at least 3 days following the single injection. Serum tilmicosin levels are a poor indicator of total body tilmicosin. The lung/serum tilmicosin ratio in favor of lung tissue appeared to equilibrate by 3 days post-injection at approximately 60. In a study with radioactive tilmicosin, 24% and 68% of the dose was recovered from urine and feces respectively over 21 days. After a single subcutaneous injection of Micotil at 10mg/kg of body weight, tilmicosin concentrations in excess of 4 µg/mL were maintained in the alveolar macrophages and neutrophils of most cattle for at least 10 days. The clinical relevance of these findings has not been determined.

Microbiology: Tilmicosin has an *in vitro* antibacterial spectrum that is predominantly Gram-positive with activity against certain Gram-negative microorganisms. *In vitro* activity against several *Mycoplasma* species has also been observed.

Effectiveness: In a multi-location field study, 1508 calves with naturally occurring BRD were treated with Micotil. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude and activity, normal respiration, and a rectal temperature of 41.0°F on Day 13. The cure rate was significantly higher ($P=0.004$) in Micotil-treated calves (63.1%) compared to saline-treated calves (29.2%). During the treatment phase of the study, there were 10 BRD-related deaths in the Micotil-treated calves compared to 47 in the saline-treated calves.

Animal Safety: A safety study was conducted in feeder calves receiving subcutaneous doses of 20, 30, 40, or 60 mg/kg of body weight, injected 3 times at 72-hour intervals. Death was not seen in any of the treatment groups. Injection site swelling and mild hemorrhage at the injection site were seen in animals in all dosage groups. Lesions were described as being generally more severe and occurred at higher frequency rates in the animals treated with higher doses of tilmicosin. Lameness associated with the injection site was noted in two of twenty-four animals (one animal in the 30 mg/kg body weight treatment group and one animal in the 60 mg/kg treatment group). No other drug related lesions were observed macroscopically or microscopically. Decreases in food and water consumption were noted in all treatment groups compared to the control group.

A separate safety study conducted in feeder calves, subcutaneous doses of 10, 30, or 50 mg/kg of body weight, injected 3 times at 72-hour intervals did not cause any deaths. Edema at the site of injection was noted. The only lesion observed at necropsy was minimal myocardial necrosis in some animals dosed at 50 mg/kg.

In an additional safety study, subcutaneous doses of 150 mg/kg body weight injected at 72-hour intervals resulted in death of two of the four treated animals. Edema was marked at the site of injection. Minimal myocardial necrosis was the only lesion observed at necropsy. Deaths of cattle have been observed with a single intravenous dose of 5 mg/kg of body weight.

In sheep, single subcutaneous injections of 10 mg/kg body weight did not cause any deaths and no adverse effects of tilmicosin were observed on blood pressure, heart rate, or respiratory rate.

Toxicology: The heart is the target of toxicity in laboratory and domestic animals given Micotil by oral or parenteral routes. The primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotropy). Cardiovascular toxicity may be due to calcium channel blockade.

Upon subcutaneous injection, the acute median lethal dose of tilmicosin in mice is 97 mg/kg, and in rats is 185 mg/kg of body weight. Given orally, the median lethal dose is 800 mg/kg and 2250 mg/kg body weight in fasted and nonfasted rats, respectively. No compound-related lesions were found at necropsy.

In dogs, intravenous calcium offset Micotil-induced tachycardia and negative inotropy, restoring arterial pulse pressure. Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. β -adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs.

In monkeys, a single intramuscular dose of 10 mg/kg body weight caused no signs of toxicity. A single dose of 20 mg/kg body weight caused vomiting and 30 mg/kg body weight caused the death of the only monkey tested.

In swine, intramuscular injection of 10 mg/kg body weight caused increased respiration, emesis, and a convulsion. 20 mg/kg body weight resulted in mortality in 3 of 4 pigs, and 30 mg/kg caused the death of all 4 pigs tested. Injection of 4.5 and 5.6 mg/kg body weight intravenously followed by epinephrine, 1 mL (1:1000) intravenously 2 to 6 times, resulted in death of all pigs injected. Pigs given 4.5 mg/kg and 5.6 mg/kg body weight intravenously with no epinephrine all survived. These results suggest intravenous epinephrine may be contraindicated.

Results of genetic toxicology studies were all negative. Results of teratology and reproduction studies in rats were negative. The no effect level in dogs after daily oral doses for up to one year is 4 mg/kg of body weight.

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

Conservar a 86°F (30°C). Proteger de la luz solar directa.

How Supplied: Micotil is supplied in 100 mL and 250 mL multi-dose amber glass bottles.

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

Revised January 2010

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V01-03-2010