

MICOTIL 300- tilmicosin phosphate injection, solution

Elanco

Micotil® 300 Injection

Tilmicosin Injection, USP

NADA 140-929, Approved by FDA

AH0230

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. Do not use in lambs less than 15 kg body weight. Intravenous injection in cattle or sheep will be fatal. 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.

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.

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 $\mu\text{g/mL}$) in serum beyond 3 days. However, lung concentrations of tilmicosin remained above the tilmicosin MIC 95% of 3.12 $\mu\text{g/mL}$ 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 10 mg/kg of body weight, tilmicosin concentrations in excess of 4 $\mu\text{g/mL}$ 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 <104°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 dose 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. B-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 body weight caused the death of all 4 pigs tested. Injection of 4.5 and 5.6 mg/kg body weight intravenously followed by epinephrine, 1mL (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.

How Supplied:

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

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Manufactured for:

Elanco Animal Health

A Division of Eli Lilly and Company

Indianapolis, IN 46285, USA

Revised JANUARY 2010

Micotil® 300

AH0230

PA9980DEAMX

SAFE HANDLING PRACTICES WHEN USING

MICOTIL® 300 TILMICOSIN INJECTION, USP

Please read this information before you start using Micotil. This information is a summary and is not intended to take the place of discussions with your veterinarian. Micotil can only be prescribed by a licensed veterinarian who has information specific to your operation. You should discuss with your veterinarian how to use Micotil, human warnings associated with the product and recommended safe handling and use practices. For emergency medical information call 1-800-722-0987 or 1-800-428-4441. If you have any questions about Micotil, talk with your veterinarian or call Elanco at 1-800-428-4441. To report an adverse drug event contact Elanco at 1-800-428-4441.

1. WHAT ARE THE POSSIBLE EFFECTS OF ACCIDENTAL HUMAN INJECTION?

Human injections of Micotil have been associated with fatalities. Clinical signs from human exposure include off taste in the mouth, nausea, headache, dizziness, rapid heart rate, chest pain, anxiety or lightheadedness. Local reactions such as injection site pain, bleeding, swelling or inflammation have been reported.

2. WHAT SHOULD I DO IN THE CASE OF ACCIDENTAL HUMAN INJECTION?

- Immediately seek medical attention.
- Apply ice or cold pack to injection site, while avoiding direct contact with the skin, and transport immediately to a hospital.
- Call 1-800-722-0987 or 1-800-428-4441 for further emergency information.

3. WHAT SHOULD MY PHYSICIAN KNOW IN THE CASE OF ACCIDENTAL HUMAN INJECTION?

- The cardiovascular system is the target of toxicity and should be monitored closely.
- Cardiovascular toxicity may be due to calcium channel blockade.
- Intravenous calcium administration reversed the cardiovascular effects of Micotil in dogs and may provide benefit in patients exhibiting low blood pressure (hypotension) or rapid heart rate (tachycardia).
- Dobutamine improved some of the cardiac function in dogs given Micotil.
- Epinephrine increased the toxicity of Micotil in pigs, resulting in death.
- Propranolol (a beta-adrenergic antagonist), further decreased cardiac function in dogs given Micotil.
- The active ingredient in Micotil is tilmicosin phosphate and persists in tissue for several days.
- Call 1-800-722-0987 or 1-800-428-4441 for further emergency information.

4. WHAT ARE THE PROPER WAYS TO HANDLE AND STORE MICOTIL?

- Store at or below 86°F (30°C), out of direct sunlight, in a safe location, not easily accessible to

the general public.

- Read, understand and follow all label use directions.
- Keep the needle capped until ready to use.
- Never carry a loaded syringe with an attached needle in pocket or clothing.
- Wash hands thoroughly with soap and water after handling.

5. **WHAT ARE THE PROPER METHODS FOR ADMINISTERING MICOTIL?**

- Properly restrain animals prior to administration.
- Work in a team, or if alone, advise someone of your location and how long you plan to be there.
- For subcutaneous use. Do not use in automatically powered syringes.
- Use a 1/2-inch to 5/8-inch, 18- to 16-gauge needle.
- With a single hand on the syringe, insert the needle subcutaneously, at a top-down angle, while avoiding penetration of underlying muscle.
- 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.
- Administer a single subcutaneous dose of 1.5 mL to 3.0 mL of Micotil per 100 lbs of body weight, in either of the two areas noted in the adjacent drawing.



- For beef cattle, Beef Quality Assurance recommends injection site 1, unless this site is inaccessible or places the operator in a potentially dangerous situation.
- Ensure proper disposal of sharp needles and syringes.
- Wash hands thoroughly with soap and water after administration.
- Do not administer intravenously (IV) as IV administration will be fatal.
- Intramuscular injection will cause a local reaction, which may result in trim loss.
- Do not inject more than 10 mL per injection site.
- Do not use in lambs less than 15 kg body weight.

Issued January, 2010

Elanco Animal Health

- **A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA**

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PA9980DEAMX (V06-01-2010)

Principal Display Panel - 100 mL Bottle Label

Elanco® AH230-82X

For use in Cattle and Sheep Only

Micotil® 300

Tilmicosin Injection, USP

300 mg tilmicosin, USP as tilmicosin phosphate per mL

™

Do Not Use in Automatically Powered Syringes

NADA 140-929, Approved by FDA

UPC 7 2780420213

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.

Elanco®, Micotil® and the diagonal bar are trademarks of Eli Lilly and Company.
To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

Principal Display Panel - 100 mL Carton Label

Elanco® AH0230-82X

For use in Cattle and Sheep Only

Micotil® 300

Tilmicosin Injection, USP

300 mg tilmicosin, USP as tilmicosin phosphate per mL

TM

Do Not Use in Automatically Powered Syringes

Caution: Federal (USA) law restricts the 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.

NADA 140-929

Approved by FDA

UPC 7 27804 202132 100 mL

Fig. 107



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 Mico®-induced tachycardia and negative inotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by Mico® in dogs. β -adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Mico® in dogs. Epinephrine potentiated lethality of Mico® 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 1-800-722-6867 o 1-800-428-4441. Evite el contacto con los ojos.

Manufactured for:
Elanco Animal Health
A Division of Eli Lilly and Company
Indianapolis, IN 46285, USA
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To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

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 Mico®. La dobutamina compensó parcialmente los efectos inotrópicos negativos inducidos por Mico® en perros. Los antagonistas β -adrenérgicos, como propranolol, exacerbó el inotropismo negativo de Mico® en los perros. La epinefrina potenció la letalidad de Mico® en cerdos. Este antibiótico persiste en los tejidos por varios días.

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.

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.

Precautions: Read accompanying literature fully before use. Intramuscular injection will cause a local reaction which may result in loss of edible tissue at slaughter. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined.
Storage Conditions: Store at or below 80°F (30°C). Protect from direct sunlight.
Conserve a 80°F (30°C).
Proteja de la luz solar directa.

Elanco® AH0230-B2X



Do Not Use in Automatically Powered Syringes. No Administrar con Jeringas Accionadas Automáticamente.

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.

NADA 140-929
Approved by FDA
UPC 7 27804 20213 2 100 mL

Indications: For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Aerophilus somni*. For the treatment of ovine respiratory disease (ORD) associated with *Mannheimia haemolytica*. 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 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 shoulder and over the ribs.

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

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 1-800-722-6867 or 1-800-428-4441. Avoid contact with eyes.



7 27804 20213 2



Principal Display Panel - 250 mL Bottle Label

Elanco® AH0230-38W

For use in Cattle and Sheep Only

Micotil® 300

Tilmicosin Injection, USP

300 mg tilmicosin, USP as tilmicosin phosphate per mL

TM

Do Not Use in Automatically Powered Syringes

Caution: Federal (USA) law restricts the 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: For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*. For the treatment of ovine respiratory disease (ORD) associated with *Mannheimia haemolytica*. For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*.

NADA 140-929, Approved by FDA

UPC 7 27804 202132 250 mL

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MICOTIL 300			
tilmicosin phosphate injection, solution			
Product Information			
Product Type	PRESCRIPTION ANIMAL DRUG	Item Code (Source)	NDC:0986-0230
Route of Administration	SUBCUTANEOUS		
Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
TILMICOSIN PHOSPHATE (UNII: SMH7U1S683) (TILMICOSIN - UNII:XL4103X2E3)	TILMICOSIN PHOSPHATE	300 mg in 1 mL	
Inactive Ingredients			
Ingredient Name			Strength
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)			
WATER (UNII: 059QF0K00R)			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0986-0230-02	1 in 1 CARTON		
1		100 mL in 1 BOTTLE, GLASS		
2	NDC:0986-0230-03	250 mL in 1 BOTTLE, GLASS		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA140929	02/19/2010	

Labeler - Elanco (807447169)

Establishment

Name	Address	ID/FEI	Business Operations
Norbrook Laboratories Limited		232880554	MANUFACTURE

Establishment

Name	Address	ID/FEI	Business Operations
Evonik Corporation		130890994	API MANUFACTURE

Revised: 4/2014

Elanco