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Date of Approval:
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FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-929

MICOTIL 300

(tilmicosin phosphate)

To provide user safety information on the product labeling related to the mechanism of toxicity and medical intervention.

Sponsored by:
Elanco Animal Health,
A Division of Eli Lilly & Co.

200.5-140-929

FOIS 1

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1. GENERAL INFORMATION:

a. File Number:	NADA 140-929
b. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
c. Established Name:	Tilmicosin phosphate
d. Proprietary Name:	MICOTIL 300
e. Dosage Form:	Injectable solution
f. How Supplied:	50 mL, 100 mL, and 250 mL glass vials
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	300 mg/mL
i. Route of Administration:	Subcutaneous injection
j. Species/Class:	Cattle (beef and non-lactating dairy), and sheep
k. Recommended Dosage:	10 mg/kg body weight (BW)(1.5 mL per 100 lb BW), administered once
l. Pharmacological Category:	Antimicrobial
m. Indications:	For the treatment of bovine respiratory disease (BRD) and ovine respiratory disease (ORD) associated with *Mannheimia* (*Pasteurella*) *haemolytica*. For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia* (*Pasteurella*) *haemolytica*.
n. Effect of Supplement:	To provide user safety information on the product labeling related to the mechanism of toxicity and medical intervention.

2. *EFFECTIVENESS:*

The Center for Veterinary Medicine (CVM) did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 140-929 (approved March 24, 1992), and the FOI Summary for a supplemental approval of NADA 140-929 dated December 30, 1996, contain summaries of studies that demonstrate the effectiveness of tilmicosin for the labeled indications in cattle. The FOI Summary for the supplemental approval of NADA 140-929 dated September 4, 2002, contains a summary of studies that demonstrate the effectiveness of tilmicosin for the labeled indication in sheep.

3. *TARGET ANIMAL SAFETY:*

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 140-929 (approved March 24, 1992) contains a summary of target animal safety studies for cattle. The FOI Summary for the supplemental approval of NADA 140-929 dated September 4, 2002, contains a summary of the target animal safety study for sheep.

4. *HUMAN FOOD SAFETY:*

CVM did not require human food safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 140-929 (approved March 24, 1992) contains a summary of human food safety studies for cattle. The FOI Summary for the supplemental approval of NADA 140-929 dated September 4, 2002, contains a summary of the human food safety studies for sheep.

5. *USER SAFETY:*

Human warnings are provided on the product labeling as follows:

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 1-317-276-2000. 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.

6. *AGENCY CONCLUSIONS:*

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that MICOTIL 300 (tilmicosin phosphate), when administered as a subcutaneous injection, is safe and effective for the treatment of bovine respiratory disease (BRD) and ovine respiratory disease (ORD) associated with *Mannheimia* (*Pasteurella*) *haemolytica*, and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia* (*Pasteurella*) *haemolytica*.

Labeling continues to restrict this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable laypersons to appropriately diagnose and subsequently use this product to treat BRD and ORD, (b) administration by other than approved routes and dosages, or uses in species other than cattle and sheep can cause signs of toxicity, including death, and (c) there is a potential danger to the person administering the product if it is accidentally self injected or to other persons if it is accidentally injected. Because of these effects, extensive warning and caution statements are provided in the labeling which are deemed to be adequate to protect users from accidental injection and to discourage extralabel use.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

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

No patents were submitted with this application.

7. *ATTACHMENTS:*

Facsimile labeling is attached as indicated below.

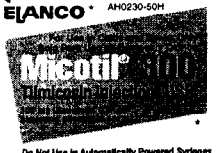
a. MICOTIL 300 – 50 mL vial label and insert
b. MICOTIL 300 – 50 mL carton
c. MICOTIL 300 – 100 mL vial label and insert
d. MICOTIL 300 – 100 mL carton
e. MICOTIL 300 – 250 mL vial label and insert
f. Client Information Sheet (English)
g. Client Information Sheet (Spanish)

YL0073MOCKUP_P2.qxd 10/11/05 2:45 PM Page 1

FRONT LABEL

PULL TO OPEN

ELANCO® AH0230-50H



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

NADA 140-929, Approved by FDA

UPC 7 2780420212 5

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

An antibiotic injection for subcutaneous use in cattle and sheep. For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*. For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

0073® CKU (DR-IV-OCT 05)

DUMMY CODE

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 1-800-722-9967 or 1-317-276-2000. Avoid contact with eyes.

Read Note to the Physician, Spanish translation, and other important information fully before use.
Lea la Nota para el Médico, traducida al Español, y otra información importante antes de usarse.

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

50 mL

Lot

Exp Date

DOTTED LINES INDICATE OVERPRINT AREA ONLY AND ARE NOT TO BE PRINTED

REVERSE SIDE OF FRONT LABEL

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 1-317-276-2000. Evite el contacto con los ojos

*Elanco®, Micotil® and the diagonal color 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

Revised OCTOBER 2005

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

AH0230

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

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 1-317-276-2000. 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.

PRECAUTIONS Read accompanying literature fully before use. Do Not Administer to Swine. Injection in Swine Has Been Shown to be Fatal. Intramuscular injection will cause a local reaction which may result in trim loss. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined. The safety of tilmicosin has not been established for sheep with a body weight of less than 15 kg

How Supplied: Micotil is supplied in 50 mL, 100 mL and 250 mL multidose amber glass bottles

Storage: Store at or below 86°F (30°C). Protect from direct sunlight.
Conservar a 86°F (30°C). Protejar de la directa luz solar

*Elanco®, Micotil® and the diagonal color bar are trademarks of Eli Lilly and Company

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 but is transient and usually *mild*

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 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 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older Use of tilmicosin in this class of cattle may cause milk residues *Do not use in lactating ewes if the milk is intended for human consumption*

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 numeros de teléfono para emergencias medicas son 1-800-722-0987 ó 1-317-276-2000. 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 compensa la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensa parcialmente los efectos inotrópicos negativos inducidos por Micotil en perros. Los antagonistas β-adrenergicos, como propranolol, exacerbaron el inotropismo negativo de Micotil en los perros. La epinefrina potenció la letalidad de Micotil en cerdos. Este antibiotico persiste en los tejidos por varios dias

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

Pharmacology. A single subcutaneous injection of Micotil®300 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 (Pasteurella) 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

Directions – Inject Subcutaneously in Cattle and Sheep Only. *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 15 mL per injection site
Do not use in lambs less than 15 kg body weight
If no improvement is noted within 48 hours, the diagnosis should be reevaluated

In swine intramuscular injection of 10 mg/kg caused increased respiration, emesis and a convulsion, 20 mg/kg 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 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 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

In cattle, subcutaneous doses of 10, 30 and 50 mg/kg of body weight, each injected 3 times at 72 hour intervals did not cause any deaths As expected, edema at the site of injection was noted The only lesion observed at necropsy was minimal myocardial necrosis in some animals in the 50 mg/kg group Subcutaneous doses of 150 mg/kg injected at 72-hour intervals resulted in deaths 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

For Subcutaneous Use in Cattle and Sheep Only. Do Not Use in Automatically Powered Syringes.

Solo Para Uso Subcutaneo en Bovinos y Ovinos No Administrar con Jeringas Accionadas Automáticamente.

Indications: Micotil®300 is indicated for the treatment of bovine respiratory disease (BRD) and ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*
Micotil®300 is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

Description. Micotil®300 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

Actions: Activity – Tilmicosin has an *in-vitro*** antibacterial spectrum that is predominantly gram-positive with activity against certain gram-negative microorganisms. Activity against several mycoplasma species has also been detected.

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

Microorganism	MIC** (µg/mL)
Mannheimia (Pasteurella) haemolytica	3.12
Pasteurella multocida	6.25
Histophilus somni	6.25
Mycoplasma dispar	0.097
M. bovirhinis	0.024
M. bovoculi	0.048

**The clinical significance of this *in-vitro* data in cattle and sheep has not been demonstrated.

Toxicology: The heart is the target of toxicity in laboratory and domestic animals given Micotil®300 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 injection subcutaneously, 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 600 mg/kg and 2250 mg/kg 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 caused no signs of toxicity. A single dose of 20 mg/kg caused vomiting and 30 mg/kg caused the death of the only monkey tested.

BASE LABEL

ELANCO® AH0230-50H

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

NADA 140-929, Approved by FDA
UPC 7 2780420212 5

50 mL

CAUTION *Federal (USA) law* restricts this drug to use by or on the order of a licensed veterinarian

An antibiotic injection for subcutaneous use in cattle and sheep For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica* For the control of *respiratory disease in cattle* at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

0073 CKU 1 (DR IV-OCT 05)

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 1-866-722-0867 or 1-317-276-2000 Avoid contact with eyes**

Read Note to the Physician, Spanish translation, and other important information fully before use
Lee la Nota para el Médico, traducida al Español, y otra información importante antes de usarse

Manufactured for Elanco Animal Health
A Division of Eli Lilly and Company
Indianapolis, IN 46285, USA
Literature for this product should be attached If it is missing, call 1-800-428-4441
La literatura para este producto debe encontrarse anexa Si faltase llamar al 1-800-428-4441

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SH8053MOCK1P
(DR-III-OCT-05)

Exp Date:

Lot

50 mL

MICOTIL®

ELANCO* AH0230-50H

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 1-317-276-2000. 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 compensa la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensa parcialmente los efectos inotrópicos negativos inducidos por Micotil en perros. Los antagonistas ß-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.

*Elanco®, Micotil®, and the diagonal color bar are trademarks of Eli Lilly and Company

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

Directions: Inject Subcutaneously in Cattle and Sheep Only. Administer a single subcutaneous dose of 10 mg/kg body weight (1 mL/30 kg or 1.5 mL per 100 lbs) Do not inject more than 15 mL per injection site. Do not use in lambs less than 15 kg body weight. 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 but is transient and usually mild.

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 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 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Do not use in lactating ewes if the milk is intended for human consumption.

PRECAUTIONS: Read accompanying literature fully before use. Do Not Administer to Swine. Injection in Swine Has Been Shown to be Fatal. Intramuscular injection will cause a local reaction which may result in trim loss. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined. The safety of tilmicosin has not been established for sheep with a body weight of less than 15 kg.

Storage: Store at or below 86°F (30°C) Protect from direct sunlight.
Conservar a 86°F (30°C) Protejar de la directa luz solar

ELANCO* AH0230-50H

Micotil®

*

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

An antibiotic injection for subcutaneous use in cattle and sheep For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica* For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

NADA 140-929
Approved by FDA

50 mL

7 27804 20212 5

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 skin. Emergency medical telephone numbers are 1-800-722-0987 or 1-317-276-2000. 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 ioeotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil. Epinephrine potentiated lethality of Micotil in pigs. This antibiotic persists in tissues for several days.

To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441

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

PULL TO OPEN

ELANCO® AH0230 82X

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

NADA 140-929, Approved by FDA
UPC 7 27804202132

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

An antibiotic injection for subcutaneous use in cattle and sheep For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*. For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

0083¹¹, CKUF (DR IV OCT 05)

DUMMY CODE

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 1-317-276-2000 Avoid contact with eyes

Read Note to the Physician, Spanish translation, and other important information fully before use.
Lea la Nota para el Médico, traducida al Español, y otra información importante antes de usarse.

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

100 mL

Lot

Exp Date

REVERSE SIDE OF FRONT LABEL

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 1-317-276-2000. Evite el contacto con los ojos.

*Elanco®, Micotil® and the diagonal color 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

PRECAUTIONS: Read accompanying literature fully before use. Do Not Administer to Swine. Injection in Swine Has Been Shown to be Fatal. Intramuscular injection will cause a local reaction which may result in trim loss. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined. The safety of tilmicosin has not been established for sheep with a body weight of less than 15 kg.

How Supplied: Micotil is supplied in 50 mL, 100 mL and 250 mL multidose amber glass bottles

Storage: Store at or below 86°F (30°C) Protect from direct sunlight
Conservar a 86°F (30°C) Protejar de la directa luz solar.

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Revised OCTOBER 2005

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

AH0230

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

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 1-317-276-2000. 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. ß-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 1-317-276-2000. Evite el contacto con los ojos.

Directions – Inject Subcutaneously in Cattle and Sheep Only. 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 15 mL per injection site
Do not use in lambs less than 15 kg body weight.
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 but is transient and usually mild.

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 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 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Do not use in lactating ewes if the milk is intended for human consumption.

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

In cattle, subcutaneous doses of 10, 30 and 50 mg/kg of body weight, each injected 3 times at 72-hour intervals did not cause any deaths As expected, edema at the site of injection was noted The only lesion observed at necropsy was minimal myocardial necrosis in some animals in the 50 mg/kg group Subcutaneous doses of 150 mg/kg injected at 72-hour intervals resulted in deaths 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 dose did not cause any deaths and no adverse effects of tilmicosin were observed on blood pressure, heart rate, or respiratory rate

Pharmacology: A single subcutaneous injection of Micotil®300 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 (Pasteurella) 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

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 compensa la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensa parcialmente los efectos inotrópicos negativos inducidos por Micotil en perros. Los antagonistas ß-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.

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

Indications: Micotil®300 is indicated for the treatment of bovine respiratory disease (BRD) and ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*. Micotil®300 is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

Description: Micotil®300 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

Actions: Activity – Tilmicosin has an *in-vitro*** antibacterial spectrum that is predominantly gram-positive with activity against certain gram-negative microorganisms Activity against several mycoplasma species has also been detected.

Ninety-five percent of the *Mannheimia (Pasteurella) haemolytica* isolates were inhibited by 3 12 µg/mL or less

Microorganism	MIC** (µg/mL)
Mannheimia (Pasteurella) haemolytica	3 12
Pasteurella multocida	6 25
Histophilus somni	6.25
Mycoplasma dispar	0 097
M bovirhinis	0 024
M bovoculi	0 048

**The clinical significance of this *in-vitro* data in cattle and sheep has not been demonstrated

Toxicology: The heart is the target of toxicity in laboratory and domestic animals given Micotil®300 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 injection subcutaneously, 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 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 ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs.

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

In swine, intramuscular injection of 10 mg/kg caused increased respiration, emesis, and a convulsion, 20 mg/kg 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 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 intravenously with no epinephrine all survived These results suggest intravenous epinephrine may be contraindicated.

ELANCO® AH0230 82X

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

NADA 140-929, Approved by FDA
UPC 7 2780420213 2

100 mL

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

An antibiotic injection for subcutaneous use in cattle and sheep For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica* For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

0083 · CKU (DR IV-OCT-05)

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 1-317-276-2000 Avoid contact with eyes.

Read Note to the Physician, Spanish translation, and other important information fully before use
Lea la Nota para el Médico, traducida al Español, y otra información importante antes de usarse

Manufactured for **Elanco Animal Health**
A Division of Eli Lilly and Company
Indianapolis, IN 46285, USA
Literature for this product should be attached If it is missing, call 1-800-428-4441
La literatura para este producto debe encontrarse anexa Si faltase llamar al 1-800-428-4441

Approved by:	Date:	Q.C. approved by:	Date:
Base Spec.: SHG050	Process colour reproduction may not match PANTONE-Identified solid color standards. Refer to current PANTONE		

100% PRIN

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BLACK

ELANCO* AH0230-82X

Micotil®

100 mL

Lot

Exp Date

7 27804 20213 2

To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

*Elanco®, Micotil®, and the diagonal color bar are trademarks of Eli Lilly and Company.

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

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.

Directions: Inject Subcutaneously in Cattle and Sheep Only. Administer a single subcutaneous dose of 10 mg/kg body weight (1 mL/30 kg or 1.5 mL per 100 lbs.). Do not inject more than 15 mL per injection site. Do not use in lambs less than 15 kg body weight. 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 but is transient and usually mild.

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 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 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Do not use in lactating ewes if the milk is intended for human consumption.

PRECAUTIONS: Read accompanying literature fully before use. Do Not Administer to Swine. Injection in Swine Has Been Shown to be Fatal. Intramuscular injection will cause a local reaction which may result in trim loss. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined. The safety of tilmicosin has not been established for sheep with a body weight of less than 15 kg.

Storage: Store at or below 86°F (30°C). Protect from direct sunlight.
Conservar a 86°F (30°C) Protejar de la directa luz solar

ELANCO* AH0230-82X

Micotil®

*

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.
An antibiotic injection for subcutaneous use in cattle and sheep. For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica*
For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*.

NADA 140-929
Approved by FDA

100 mL

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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 1-317-276-2000. Evite el contacto con los ojos.

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BASE LABEL

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

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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 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

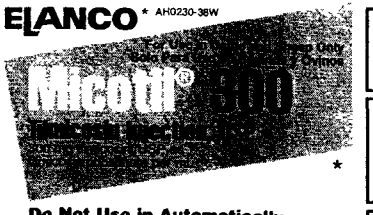
RESIDUE WARNINGS· Animals intended for human consumption must not be slaughtered within 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Do not use in lactating ewes if the milk is intended for human consumption.

PRECAUTIONS: Read accompanying literature fully before use. Do Not Administer to Swine. Injection in Swine Has Been Shown to be Fatal. Intramuscular injection will cause a local reaction which may result in trim loss. The effects of tilmicosin on bovine and ovine reproductive performance, pregnancy and lactation have not been determined. The safety of tilmicosin has not been established for sheep with a body weight of less than 15 kg.

Storage. Store at or below 86°F (30°C) Protect from direct sunlight Conservar a 86°F (30°C) Protejar de la directa luz solar

0064 CKU (DR-IV-OCT-05)

ELANCO * AH0230-38W



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

An antibiotic injection for subcutaneous use in cattle and sheep For the treatment of bovine respiratory disease (BRD) or ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica* For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica*

NADA 140-929, Approved by FDA

UPC 7 2780420214 9

250 ml

*Elanco® Micotil® and the diagonal color 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

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 1-317-276-2000 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. ß-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.

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Manufactured for **Elanco Animal Health**
A Division of Eli Lilly and Company, Indianapolis, IN 46285, USA
Literature for this product should be attached If it is missing call 1-800-428-4441
La literatura para este producto debe encontrarse anexa Si faltase llamar al 1-800-428-4441

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FRONT LABEL

PULL TO OPEN

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

Directions Inject Subcutaneously in Cattle and Sheep Only. Administer a single subcutaneous dose of 10 mg/kg body weight (1 mL/30 kg or 1 5 mL per 100 lbs) Do not inject more than 15 mL per injection site Do not use in lambs less than 15 kg body weight If no improvement is noted within 48 hours, the diagnosis should be reevaluated

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0064 CKU (DR-IV-OCT-05)

ELANCO* AH0230-38W

For Use in Cattle and Sheep Only
Solo Para Uso en Bovinos y Ovinos

Micotil® 300

Tilmicosin Injection, USP

300 mg tilmicosin, USP as tilmicosin phosphate per mL *

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

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NADA 140-929, Approved by FDA

UPC 7 2780420214 9

250 ml

*Elanco® Micotil® and the diagonal color bar are trademarks of Eli Lilly and Company

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

DUMMY CODE

Lot

Exp Date

DOTTED LINES INDICATE OVERPRINT AREA ONLY AND ARE NOT TO BE PRINTED

*Elanco®, Micotil® and the diagonal color bar are trademarks of Eli Lilly and Company

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

Revised OCTOBER 2005

AH0230

NADA 140-929, Approved by FDA

Micotil®300

Tilmicosin Injection, USP

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

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For Subcutaneous Use in Cattle and Sheep Only. Do Not Use in Automatically Powered Syringes.

Solo Para Uso Subcutaneo en Bovinos y Ovinos. No Administrar con Jeringas Accionadas Automaticámente.

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 28 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of tilmicosin in this class of cattle may cause milk residues. Do not use in lactating ewes if the milk is intended for human consumption.

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How Supplied: Micotil is supplied in 50 mL, 100 mL and 250 mL multidose amber glass bottles

Storage: Store at or below 86°F (30°C). Protect from direct sunlight.
Conservar a 86°F (30°C). Protejar de la directa luz solar

Pharmacology: A single subcutaneous injection of Micotil®300 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 (Pasteurella) 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

Directions – Inject Subcutaneously in Cattle and Sheep Only. 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 15 mL per injection site

Do not use in lambs less than 15 kg body weight.

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 but is transient and usually mild

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.

Indications: Micotil®300 is indicated for the treatment of bovine respiratory disease (BRD) and ovine respiratory disease (ORD) associated with *Mannheimia (Pasteurella) haemolytica* Micotil®300 is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica.*

Description: Micotil®300 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

Actions: Activity – Tilmicosin has an *in-vitro*** antibacterial spectrum that is predominantly gram-positive with activity against certain gram-negative microorganisms. Activity against several mycoplasma species has also been detected.

Ninety-five percent of the *Mannheimia (Pasteurella) haemolytica* isolates were inhibited by 3 12 µg/mL or less

Microorganism	MIC** (µg/mL)
Mannheimia (Pasteurella) haemolytica	3.12
Pasteurella multocida	6.25
Histophilus somni	6.25
Mycoplasma dispar	0.097
M bovirhinis	0.024
M. bovoculi	0.048

**The clinical significance of this *in-vitro* data in cattle and sheep has not been demonstrated.

Toxicology: The heart is the target of toxicity in laboratory and domestic animals given Micotil®300 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 injection subcutaneously, 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 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 ß-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs

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

In swine, intramuscular injection of 10 mg/kg caused increased respiration, emesis, and a convulsion, 20 mg/kg 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 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 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

In cattle, subcutaneous doses of 10, 30 and 50 mg/kg of body weight, each injected 3 times at 72 hour intervals did not cause any deaths. As expected, edema at the site of injection was noted. The only lesion observed at necropsy was minimal myocardial necrosis in some animals in the 50 mg/kg group. Subcutaneous doses of 150 mg/kg injected at 72-hour intervals resulted in deaths. 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 dose did not cause any deaths and no adverse effects of tilmicosin were observed on blood pressure, heart rate, or respiratory rate.

Height - 46mm Height - 46mm Height - 48mm

Width - 69mm

Width - 72mm

Width - 75mm

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 1-317-276-2000 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 1-317-276-2000 for further emergency information

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

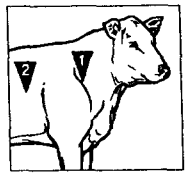
   - The cardiovascular system is the target of toxicity and should be monitored closely
   - Cardiovascular toxicity may be due to calcium channel blockade
   - Intravenous calcium administration reversed the cardiovascular effects of Micotil in dogs and may provide benefit in patients exhibiting low blood 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 1-317-276-2000 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 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 15 mL per injection site.
   - Do not use in lambs less than 15 kg body weight.

Issued October, 2005

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Indianapolis, IN 46285, USA

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PA9082MOCKUP DR-V-OCT-05

DUMMY CODE

AH0230

Micotil® 300

IMPORTANT CLIENT INFORMATION
CUIDADO

PA9082MOCKUP DR-V-OCT-05

DUMMY CODE

Height - 46mm Height - 46mm Height - 48mm

Width - 75mm Width - 72mm Width - 69mm

PRÁCTICAS DE MANEJO SEGURO CUANDO SE UTILIZA

MICOTIL® 300 TILMICOSINA INYECTABLE, USP

Por favor lea esta información antes de comenzar a utilizar Micotil. Esta información es un resumen y no pretende sustituir que lo discuta con su veterinario. Micotil solamente puede ser prescrito por un médico veterinario autorizado que tenga la información específica de su operación. Usted deberá discutir con su veterinario como usar Micotil, las *advertencias para humanos* asociadas con este producto y el manejo seguro y prácticas de uso que se recomiendan. Para emergencias de información médica llame al 1-800-722-0987 o 1-317-276-2000. Si tiene alguna pregunta acerca de Micotil, hable con su veterinario o llame a Elanco al teléfono 1-800-428-4441. Para reportar algún evento adverso con el *medicamento póngase en contacto* con Elanco al 1-800-428-4441.

1. **¿CUÁLES SON LOS POSIBLES EFECTOS DE UNA INYECCIÓN ACCIDENTAL EN EL SER HUMANO?**

   Las inyecciones de Micotil al ser humano se asociaron con fallecimientos. Los signos clínicos de la exposición humana incluyen sabor desagradable en la boca, náuseas, dolor de cabeza, mareos, latidos rápidos, dolor en el pecho, ansiedad o atontamiento Se han comunicado reacciones locales como dolor, sangrado tumefacción o inflamación en el sitio de la inyección

2. **¿QUÉ DEBO HACER EN CASO DE UNA INYECCIÓN ACCIDENTAL A UN SER HUMANO?**

   - Busque atención médica inmediatamente
   - Aplique hielo o una bolsa de hielo al sitio de la inyección, evitando el contacto directo con la piel, y transporte al paciente inmediatamente a un hospital.
   - Llame al 1-800-722-0987 o al 1-317-276-2000 para obtener más información de emergencia

3. **¿QUÉ DEBE SABER MI MÉDICO EN CASO DE UN INYECCIÓN ACCIDENTAL AL SER HUMANO?**

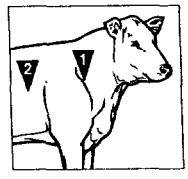
   - El sistema cardiovascular es el blanco de la toxicidad y debe vigilarse estrechamente.
   - La toxicidad cardiovascular puede deberse a bloqueo de los canales de calcio.
   - La administración intravenosa de calcio revirtió los efectos cardiovasculares de Micotil en los perros y puede ofrecer beneficios a los pacientes que presentan presión arterial baja (hipotensión) o latidos rápidos (taquicardia)
   - La dobutamina mejoró parcialmente la función cardíaca en los perros que recibieron Micotil.
   - La epinefrina aumentó la toxicidad de Micotil en los cerdos, causando muertes.
   - Propranolol (un antagonista ß-adrenérgico) disminuyó aún más la función cardíaca en perros tratados con Micotil.
   - El ingrediente activo de Micotil es el fosfato de tilmicosina, que persiste en los tejidos por varios días
   - Llame al 1-800-722-0987 o al 1-317-276-2000 para obtener más información de emergencia.

4. **¿CUÁLES SON LAS FORMAS ADECUADAS DE MANEJO Y ALMACENAMIENTO PARA MICOTIL?**

   - Almacene a temperatura de 86 °F (30 °C) o menor, fuera de la luz solar directa, en un sitio seguro que no esté fácilmente accesible al público en general.
   - Lea, entienda y cumpla con todas las instrucciones para el uso incluidas en la etiqueta.
   - Mantenga la aguja tapada hasta que esté listo para usarla.
   - Nunca lleve en el bolsillo o la ropa una jeringuilla cargada con una aguja montada.
   - Lávese las manos minuciosamente con agua y jabón después de la manipulación.

5. **¿CUÁLE SON LOS MÉTODOS ADECUADOS PARA LA ADMINISTRACIÓN DE MICOTIL?**

   - Sujete a los animales en forma apropiada antes de la administración
   - Trabaje con un equipo o bien, si está solo, avise a alguien dónde estará y por cuánto tiempo estará allí
   - Para uso subcutáneo. No utilice jeringas operadas automáticamente.
   - Utilice una aguja de 1/2-pulgada a 5/8-pulgada, del calibre 18 a 16.
   - Sujete adecuadamente a los animales antes de su administración.
   - Con una sola mano en la jeringa, inserte la aguja subcutáneamente, en un ángulo de arriba hacia abajo, evitando penetrar el músculo subyacente.
   - Para bovinos y ovinos se recomienda la inyección *subcutánea en la región* del cuello. Si no fuese accesible, inyecte debajo de la piel detrás de los hombros y sobre las costillas.
   - Administre una sola dosis subcutánea de 1,5 ml de Micotil por cada 45,4 kg de peso, en cualquiera de las dos áreas marcadas en el dibujo anexo.



   - Para bovinos de carne, Seguridad de la Calidad de la Carne recomienda la inyección en el sitio 1, a menos de que este sitio esté inaccesible para el operador o lo ponga en una situación potencialmente peligrosa.
   - Asegúrese de desechar adecuadamente las agujas filosas y las jeringuillas
   - *Lávese las manos* minuciosamente con agua y jabón después de la administración.
   - No administre por vía intravenosa (IV) ya que la administración IV causará la muerte.
   - La inyección intramuscular causará una reacción local que puede resultar en pérdidas por recorte.
   - No inyecten más de 15 ml por sitio de inyección
   - No use en corderos de menos de 15 kg de peso.

Editado en Octubre, 2005

Elanco Animal Health
Una División de
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Indianapolis, IN 46285, USA

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