Micotil® Dose and Administration Information

Indications: Micotil® is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida*. For the reduction of morbidity associated with BRD in feedlot calves, caused by *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida*, during the first 30 days in the feedlot, when administered at the time of arrival. For the treatment of pneumonic pasteurellosis in lambs associated with *Mannheimia (Pasteurella) haemolytica*.

Dosage and administration:
Administer a single subcutaneous injection of 10 mg tilmicosin per kg of body weight (1 mL per 30 kg or 1.5 mL per 100 lb). Do not inject more than 10 mL per injection site.

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

Residue warning: Treated cattle must not be slaughtered for use in food for at least 28 days after the latest treatment with Micotil. Do not use in lactating dairy cattle.

Micotil dosage chart

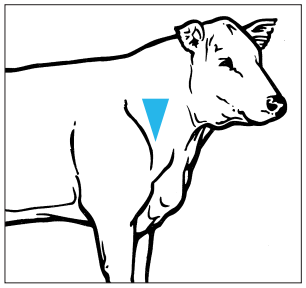
Animal weight (lb)	Micotil dosage (mL) 1.5 mL/100 lb body weight
200	3.00
300	4.50
400	6.00
500	7.50
600	9.00
700	10.50
800	12.00
900	13.50
1,000	15.00

Proper Micotil handling procedures

- Store Micotil in a secure location to prevent the risk of misuse.
- Recommended storage includes a lockable cabinet or container or a secure storage room, depending on the amount of product in inventory.
- Keep full or empty Micotil bottles, used syringes and needles out of the reach of children and the general public.
- Read, understand and follow all label use directions.
- **For subcutaneous use; do not use in automatically powered syringes.**
- Use a 1/2" to 5/8" 18- to 16-gauge needle.
- Keep a protective cover on needles until ready to use.
- Never carry loaded syringes in pocket or clothing.
- Wash hands thoroughly with soap and water after handling.

Proper Micotil administration procedures

- Properly restrain animal prior to administering Micotil.
- With a single hand on the syringe, insert the needle subcutaneously, at a top-down angle, while avoiding penetration of underlying muscle.
- 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 lb of body weight.
- Ensure proper disposal of needles, syringes and used bottles.
- If syringe is broken or damaged in any way, discontinue use immediately.
- Exercise caution and care when removing needle from syringe.
- Access to Micotil should be limited to personnel trained in safe handling and use procedures.



What to do in case of accidental self-injection

Seek immediate medical attention and:

REACH for and apply ice pack.

REFERENCE product label "Note to the physician" and/or product insert and provide to emergency medical personnel.

REMEMBER to contact Rocky Mountain Poison and Drug Center (RMPDC) at 1-800-722-0987 (select product support).

Important safety information

Before using this product, it is important to read the entire product insert, including the boxed human warning.

- Caution: Federal (Canada) 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 lactating dairy cattle. 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.
- Micotil has a pre-slaughter withdrawal time of 28 days.

Two-stage activated Sekurus™ syringe

- Developed and manufactured by Simcro™, the syringe is a patented technology with self-tenting and needle-guard features.
- The syringe reduces the chance of self-injection and withstands the most challenging environments at feedyards and stocker operations.
- To be activated, the trigger must be pulled and then the syringe pushed against the animal. Both actions must be performed for the product to be administered.
- To obtain more information about this syringe or to receive one, please consult your veterinarian or contact your Elanco representative.

For more information about Elanco products, call your Elanco sales representative or visit elanco.ca.

This is not the actual approved label. For information purposes only.

DIN 00857602

Micotil™

Tilmicosin Injection USP

Each mL contains 300 mg of tilmicosin

VETERINARY USE ONLY

Sterile

For subcutaneous use in cattle and lambs only (see pull-out label for important safety information).

Active Ingredient: tilmicosin

Non-medicinal Ingredients: Propylene glycol 25% w/v

DESCRIPTION: Micotil injection is a preconstituted solution of the antibiotic tilmicosin. Each mL contains 300 mg of tilmicosin activity; 25% propylene glycol; phosphoric acid as needed to adjust pH; and water for injection, q.s. Tilmicosin is produced semi-synthetically and is a member of the macrolide class of antibiotics.

INDICATIONS: For the treatment of bovine respiratory disease (BRD) associated with *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida*. For the reduction of morbidity associated with bovine respiratory disease (BRD) in feedlot calves, caused by *Mannheimia (Pasteurella) haemolytica* and *Pasteurella multocida*, during the first 30 days in the feedlot, when administered at the time of arrival. For the treatment of pneumonic pasteurellosis in lambs associated with *Mannheimia (Pasteurella) haemolytica*.

DOSAGE AND ADMINISTRATION: FOR SUBCUTANEOUS USE IN CATTLE. FOR SUBCUTANEOUS USE IN LAMBS GREATER THAN 15 KG BODY WEIGHT ONLY. Administer a single subcutaneous injection of 10 mg tilmicosin per kg of body weight (1 mL per 30 kg/1.5 mL per 100 lb). Do not inject more than 10 mL per injection site.

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.

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

NOTE: Swelling at the subcutaneous site of injection may be observed but is transient and usually mild.

CONTRAINDICATIONS: DO NOT ADMINISTER INTRAVENOUSLY. INTRAVENOUS INJECTION IN CATTLE AND LAMBS HAS BEEN FATAL.

DO NOT ADMINISTER TO ANIMALS OTHER THAN CATTLE OR SHEEP. INJECTION OF TILMICOSIN IN SWINE, GOATS AND NON-HUMAN PRIMATES HAS BEEN FATAL. TILMICOSIN MAY BE FATAL IN HORSES AND OTHER EQUIDS.

WARNINGS:

Treated cattle must not be slaughtered for use in food for at least 28 days after latest treatment with this drug. Do not use in lactating dairy cattle.

Treated sheep must not be slaughtered for use in food for at least 36 days after latest treatment with this drug.

HUMAN WARNINGS: Not for human use. Human injection has been associated with fatalities. 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. Do not apply ice directly to skin. For emergency medical information call 1-800-722-0987.

KEEP OUT OF REACH OF CHILDREN. AVOID CONTACT WITH EYES.

NOTE TO 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) within approximately 20 minutes. Dobutamine dose-dependently partially offset the negative inotropic effects induced by Micotil in dogs, but did not have an effect on the increased heart rate caused by Micotil. β-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs. Epinephrine potentiated lethality of Micotil in pigs. **Epinephrine is contraindicated.** This antibiotic persists in tissues for several days.

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 technical assistance or to report suspected adverse drug events, contact Elanco, Division Eli Lilly Canada Inc. at 1-800-265-5475.

ACTIVITY: Micotil 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.

In addition to its direct antibacterial action, tilmicosin may exert an anti-inflammatory effect in the lung by increasing neutrophil apoptosis and reducing the release of pro-inflammatory mediators. However, the clinical significance of this effect is unknown.

In clinical trials, BRD treatment success with Micotil was usually characterized by rapid reduction in body temperatures, less severity of clinical signs, better weight gains and reduced mortality.

TOXICOLOGY: The cardiovascular system appears to be the target of toxicity in laboratory animals and domestic livestock administered 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 injection subcutaneously, the acute median lethal dose (MLD) of tilmicosin in mice is 97 mg of activity per kg and in rats is 185 mg/kg of body weight. Given orally, the MLD of tilmicosin 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 within approximately 20 minutes. Dobutamine dose-dependently partially offset the negative inotropic effects induced by Micotil in dogs, but did not have an effect on the increased heart rate caused by Micotil. β-adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of Micotil in dogs.

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

In swine, intramuscular injection of Micotil at 10 mg/kg caused increased respiration, emesis and a convulsion, 20 mg/kg resulted in mortality in three of four pigs and 30 mg/kg caused the death of all four pigs tested. Injection of Micotil at 4.5 and 5.6 mg/kg intravenously followed by epinephrine, 1 mL (1:1000) intravenously two to six times, resulted in death of all pigs injected. All pigs given 4.5 mg/kg and 5.6 mg/kg Micotil intravenously with no epinephrine 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 of tilmicosin for up to one year is 4 mg/kg of body weight.

In cattle, subcutaneous doses of Micotil at 10, 30 and 50 mg/kg of body weight, each injected at 72-hour intervals three times, did not cause any deaths. As expected, edema at the site of injection was noted. In cattle, the only lesion observed at necropsy was minimal myocardial necrosis in the 50 mg/kg Micotil group. Subcutaneous doses of Micotil at 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 Micotil at 5 mg/kg of body weight.

In lambs, single subcutaneous doses of Micotil up to 150 mg/kg of body weight did not cause death. Deaths of lambs have been observed with a single intravenous dose of Micotil at 7.5 mg/kg body weight.

PHARMACOKINETICS: A single subcutaneous injection of Micotil at 10 mg/kg of body weight 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 three days following the single injection. Serum tilmicosin levels are a poor indicator of total body tilmicosin. The lung/serum tilmicosin ratio in favour of lung tissue appeared to equilibrate by three 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.

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

HOW SUPPLIED: Micotil is supplied in multidose amber bottles containing 300 mg of tilmicosin activity per mL.

MANUFACTURED BY: Elanco, Division Eli Lilly Canada Inc., 150 Research Lane, Suite 120, Guelph, ON N1G 4T2, Canada

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