December 22, 2005

Dear Healthcare Provider,

In April 2005, the Nebraska Regional Poison Center sent information regarding the treatment of accidental or intentional human injection of tilmicosin (Micotil 300®). The manufacturer, Elanco, has recently sent us an updated treatment guideline that highlights the potential benefits of intravenous calcium in patients with cardiovascular effects. Even though the potential benefit of calcium chloride was discussed in April, we feel it is important to highlight this information by enclosing Elanco's updated guideline and the Nebraska Regional Poison Center's treatment protocol.

All patients with parenteral exposure to tilmicosin should be immediately transported to an emergency department by EMS. Please note that the administration of intravenous calcium would be potentially beneficial when given in the field by EMS and/or in the hospital setting.

Since tilmicosin exposures have a high fatality rate, it is important that all healthcare providers who may care for exposed patients are familiar with the treatment guidelines. In addition, the Nebraska Regional Poison Center (1-800-222-1222) should be immediately contacted following all tilmicosin exposures.

Please contact me if you have any questions.

Steven A. Seifert, MD, FACMT
Medical Director
Micotil 300® = Tilmicosin

**Uses/Action:** Veterinary antibiotic used in cattle. Produces myocardial depression and ventricular arrhythmias.

**Clinical Effects:** Hypotension, chest pain, ventricular arrhythmias, and death may be seen. Effects possible with injection of less than 0.5 mL. Doses in excess of 10 mL have produced fatalities. Case fatality rate ~ 1%. Major effects involve the cardiac or respiratory systems. Tachydysrhythmias, pulmonary edema, enlarged heart, respiratory distress requiring intubation, chest pain, anxiety, agitation, local irritant effects, and death have all been reported.

**Non-Parenteral Unintentional Exposures**

1. External decontamination if dermal or ocular exposure.
2. Observe for any signs / symptoms
3. If symptoms develop → Health care facility and re-contact Poison Center immediately.

**ANY Parenteral Exposure**

1. All injection exposures to tilmicosin should be referred immediately to an ED with transport by EMS.
2. Cold packs should be used to slow absorption.
3. Basic wound care including tetanus prophylaxis prn.
4. Ax patients should be monitored for a minimum of 8 hours, with PC telephone follow-up for 24 hours.
5. Symptomatic pts. should be admitted and monitored.
6. There is no specific antidote.
7. Calcium chloride infusion was effective in reversing the cardiovascular effects of IV tilmicosin in a dog study, and may be of benefit for symptomatic patients.
8. Dobutamine or dopamine have been effective in partially offsetting hypotension from tilmicosin’s negative inotropic effect in dog studies and human case reports.
9. Beta-adrenergic antagonists, such as propranolol, should be avoided, as they exacerbate the negative inotropy of tilmicosin-induced tachycardia in dogs.
10. Epinephrine potentiated the lethality of tilmicosin in a small pig study. Routine use of epinephrine is discouraged. The potential risk-to-benefit ratio of any intervention should be determined on a case-by-case basis and by the patient’s clinical condition.

A TOXICOLOGIST IS ALWAYS AVAILABLE FOR CONSULTATIONS

STEVEN A. SEIFERT, MD
MEDICAL DIRECTOR
DATE: December 22, 2005
EXPIRES: September 30, 2006
December 15, 2005

Nebraska Regional Poison Center
8200 Dodge Street
Omaha, NE 68114

IMPORTANT DRUG WARNING & MEDICAL INFORMATION

Dear Nebraska Regional Poison Center Representative:

Elanco Animal Health, A Division of Eli Lilly and Company, manufactures the prescription animal antibiotic Micotil® (tilmicosin injection). Micotil is indicated for the treatment of bovine respiratory disease (BRD) and ovine respiratory disease (ORD) associated with Mannheimia (Pasteurella) haemolytica. It is administered as a subcutaneous injection in both cattle and sheep. United States federal law restricts this drug to use by or on the order of a licensed veterinarian.

Since Micotil’s introduction in 1992, the label has included boxed human warning advising users and physicians on safe use and medical interventions in case of self-injection. As noted, Micotil® is not for human use. Micotil injection in humans has been associated with fatalities. Elanco directs anyone responding to a human exposure event to contact Rocky Mountain Poison and Drug Center (RMPDC) toll free at 1-800-722-0987.

Elanco has recently revised the Micotil label to include results from additional in vitro and in vivo animal studies demonstrating Micotil’s cardiotoxicity may be due to calcium channel blockade. Clinical signs of tachycardia progressing to arrhythmias and hypotension are similar to those observed after overdose of dihydropyridine calcium channel blocking drugs like nifedipine. As a result of this new information the boxed human warning has been revised, with the new changes highlighted below.

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.
These and other studies are suggestive of the following:

- Intravenous (IV) calcium in the tachycardic or hypotensive patient
- Dobutamine or dopamine may partially offset Micotil's® negative inotropic effects in humans.
- Monitor cardiovascular and respiratory function.

Avoid the following:

- Beta-adrenergic antagonists, such as propranolol
- Epinephrine potentiated lethality in pigs and is contraindicated. Norepinephrine should also be avoided due to its similarity to Epinephrine.

The results of these studies and a review of human adverse drug experience reports are incorporated into the attached Micotil Intervention Guideline for Human Injections, Accidental or Intentional.

We ask that you make this information available to emergency medical personnel who may care for patients exposed to Micotil. Assistance in handling any human exposures is available by calling 1-800-722-0987 or 1-317-276-2000.

Sincerely,

Larry A. Stobbs, DVM  
Director, Regulatory Affairs  
Elanco Animal Health

Theressa J. Wright, MD  
Cardiovascular Medical Fellow I  
Eli Lilly and Company

Please see full product label, attached
Micotil® (tilmicosin injection)
Intervention Guideline for Human Injection
Accidental or Intentional

Suggested guideline for Poison Control Centers & other Emergency Medical Personnel

**There is No Antidote**

- Basic Life Support measures should be instituted immediately.
- The cardiovascular system is the target of toxicity.
- Watch for clinical signs of hypotension, tachycardia and other symptoms associated with cardiac or respiratory system dysfunction.
- Apply ice or cold pack to wound to slow absorption—no ice directly on skin.
- Regardless of the amount injected—immediate ED referral via EMS required.

**ED Referral:**

**Symptomatic Patients:**

- Provide supportive treatment as indicated, monitor cardiovascular and respiratory function and note the following:
  1. Administration of **Intravenous calcium** may provide benefit if patient is exhibiting rapid heart rate (tachycardia) or low blood pressure (hypotension). *Scientific Rationale a & b.*
  2. **Dobutamine and Dopamine** may partially offset the negative inotropic effects and tachycardia. *Scientific Rationale b.*
  3. **Avoid beta-adrenergic antagonists, such as propranolol.** *Scientific Rationale b.*
  4. **Epinephrine is contraindicated.** Norepinephrine should also be avoided due to its similarity to Epinephrine. *Scientific Rationale d.*

- Provide basic wound care. Apply ice or cold pack to slow absorption—no ice directly on the skin. Update tetanus as needed.

**Asymptomatic Patients:**

- Provide supportive and basic wound care. Apply ice or cold pack to slow absorption—no ice directly on the skin. Update tetanus as needed.
- Monitor cardiovascular and respiratory function for a minimum of 8 hours with follow up by the Poison Control Center at 1, 6, 12 and 24 hours.
- Close case after 24 hours follow up if patient remains asymptomatic.
Scientific Rationale

a. There is in vitro and in vivo evidence that Micotil is a potent calcium channel antagonist with clinical signs more similar to dihydropyridine overdose, such as nifedipine, as opposed to mixed ion channel blockers like verapamil.

➤ Administration of intravenous calcium may provide benefit if patient is exhibiting rapid heart rate (tachycardia) or low blood pressure (hypotension).

b. In dogs, intravenous calcium offset Micotil-induced tachycardia, increased arterial pulse pressure and negative inotropy. 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.

c. In monkeys, a single intramuscular dose of 10 mg/kg Micotil 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.

d. In swine, intramuscular injection of 10 mg/kg caused increased respiration, emesis, and a convolution. 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.

➤ When treating humans who have been exposed to tilmicosin, do not use beta-adrenergic antagonists or epinephrine (adrenalines) as instructed in the advanced cardiac life support (ACLS) algorithms. Norepinephrine should also be avoided due to its similarity to Epinephrine.

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Human Exposure: Signs and Symptoms Reported After Injection

- Tachycardia progressing to arrhythmias
- Hypotension (decreased blood pressure)
- Pulmonary edema
- Shortness of breath progressing to rapid respiratory rates, difficulty in breathing and/or ultimately respiratory distress requiring intubation and ventilatory support
- Chest tightness
- Enlarged heart (per chest x-ray)
- Anxiety
- Agitation
- Erythema +/- swelling and severe pain at site of injection

For the most up-to-date information, please call Rocky Mountain Poison & Drug Center at 800-722-0987, Eli Lilly & Company at 317-276-2000
Effective December, 2005
Micotil® (tilmicosin injection) Healthcare Provider FAQs

1. How does Micotil cause cardiotoxicity?
   Micotil causes negative inotropy accompanied by reflex tachycardia and vasodilation, which may lead to hypotension and reduced cardiac output leading to cardio-respiratory compromise in severe cases.

2. Is Micotil a Calcium Channel Antagonist?
   Yes. Recent in vitro data suggest that tilmicosin (the active ingredient in Micotil) is a potent antagonist of calcium channels in cardiac tissue.

3. Is intravenous calcium a physiologic antagonist?
   Yes. In animal studies, intravenous calcium chloride reversed all of the toxic effects of Micotil exposure within 20 minutes.

4. Does Micotil have any effects on potassium channels that would cause QTc prolongation, which may lead to Torsade de Pointes?
   No, our in vitro data shows substantial calcium blockade with no evidence of potassium channel inhibition at tilmicosin concentrations at or below concentrations in humans and animals that have been associated with cardiovascular toxicity. At very high concentrations, in addition to calcium blockade there is some evidence of potassium channel inhibition. However, no QTc prolongation leading to Torsade de Pointes has been reported in humans or animals following Micotil exposure.

5. Why is the use of epinephrine contraindicated in Micotil toxicity?
   Tachycardia is a frequent, cardiovascular clinical sign reported from all species exposed to toxic levels of Micotil. Epinephrine is contraindicated as it may further aggravate Micotil-induced tachycardia. A laboratory study in pigs has shown that epinephrine potentiated the lethality of Micotil.

6. Why is the use of beta blockers contraindicated in Micotil toxicity?
   Propranolol exacerbated the negative inotropy induced by Micotil in a laboratory study in conscious dogs. Other beta-blockers should be avoided as they may further aggravate Micotil-induced negative inotropy.

7. Which vasopressors are suitable to use in Micotil toxicity?
   Agents such as dopamine or dobutamine are suitable to use without aggravating Micotil-induced tachycardia and cardiac toxicity.

8. How does the canine study of Micotil intravenous exposure relate to human medical intervention for intramuscular exposure?
   The conscious canine model is considered an appropriate system to investigate Micotil induced cardiac toxicity. This work builds upon our previous efforts with this model. Using this information, health care professionals can make the most appropriate decisions for their patients.
9. **Does this information apply to all macrolide antibiotics?**

Current studies were only conducted with Micotil. *In vitro* calcium channel effects have been reported for some macrolides, however, calcium channel antagonism may not be universal to all macrolides.


10. **How long should I monitor a patient who is asymptomatic after parenteral Micotil exposure?**

Monitor cardiovascular and respiratory function for a minimum of 8 hours post exposure. Please refer to the Micotil intervention guideline: Micotil® (tilmicosin injection) Intervention Guideline for Human Injection, Accidental or Intentional

11. **How long should I monitor a patient who is symptomatic after parenteral exposure to Micotil?**

Admit and monitor the patient for 24 hours minimum. Please refer to the Micotil intervention guideline: Micotil® (tilmicosin injection) Intervention Guideline for Human Injection, Accidental or Intentional