JUDICIOUS USE OF ANTIBIOTICS FOR EFFECTIVE TREATMENT OF BOVINE RESPIRATORY DISEASE (BRD)

A Cattle Conference Recap – Sponsored by Elanco Animal Health

The following content represents a summary of AgTelePanels sponsored by Elanco Animal Health and produced by Beck Ag in June 2011. Veterinarians from across the country discussed the presence of BRD in stocker cattle production systems, the importance of using antibiotics judiciously to treat BRD and how veterinarians are helping clients optimize their antibiotic investment. Panel members for the AgTelePanel included:

- Daniel Thomson, MS, PhD, DVM, Jones Professor of Production Medicine, Kansas State University, Manhattan, KS
- W. J. Hill, DVM, Dimmitt Veterinary Clinic, Dimmit, TX
- Fred Reuter, DVM, Reuter & Reuter, Inc., El Reno, OK
- Ken Blue, DVM, Technical Consultant, Elanco Animal Health, Lawrenceburg, TN

BRD STILL A 'BIG CHALLENGE'

Bovine Respiratory Disease (BRD) is nothing new to stocker producers and their veterinarians. Backgrounding operations have always been prone to BRD for a variety of reasons, from transportation stress to the commingling of cattle from varying sources and geographies. In addition to the long-standing reasons why stocker calves are susceptible to BRD, several newer factors are also contributing to why the disease is still so prevalent.

"Looking back over the years, we've got a lot more sophisticated antibiotics for BRD now, but we don't save any more cattle from this disease. It seems to me that the sickness and the death losses are greater now than 30 years ago — probably for a couple reasons. Most of the cattle we get in are shipped in from the Southeast: Arkansas, Florida, Tennessee, Kentucky and some from south Texas and Mexico. These calves are purchased by an order buyer from an auction barn and commingled at his barn. By this time, it may be six or seven days since that calf left home, and he'd been weaned in this process. So, when we get him, he's a pretty sick guy. All this means is that at certain times in a year, our morbidities will exceed 60 percent," said W. J. Hill, DVM, from Dimmit, Texas.

To help combat the devastating effects of BRD to both the animals' health and producers' bottom lines, the use of antibiotics has long been standard in the beef cattle industry. Unfortunately, some experts report that there are consumer groups and others outside of agriculture that are not as informed about antimicrobial use in veterinary medicine.

"There are some organizations and consumer groups that have raised concerns about antibiotics in highly public forums. However, I think the average consumer has a high level of confidence in the way we raise beef, and that's largely due to the diligence of veterinarians and producers working together to judiciously use antimicrobials," said Daniel Thomson, MS, PhD, DVM, a professor at Kansas State University.

"However, when we have reports of people abusing these products and not using them appropriately, it can fuel the fire and put a shadow of doubt in the minds of our consumers. And, as veterinarians, we are the professionals who the consumer turns to when they have a question about food safety or animal welfare. So, since we're writing the prescriptions, there are going to be increased pressures and liability for veterinarians to use the appropriate antibiotics and document how they're being used," Thomson continued.

One option available to the beef industry to continue using antimicrobial drugs as judiciously as possible, while still providing effective treatment for BRD, is the Micotil® (tilmicosin injection) Flex Dose. This label allows for more flexible dosages: a range from 1.5 mL/cwt to 3.0 mL/cwt for both metaphylaxis and individual pull-and-treat therapy. The label has a pre-slaughter withdrawal time of 42 days regardless of dose.

BOVINE RESPIRATORY DISEASE CAUSES SERIOUS ECONOMIC LOSSES

- **Snowder et al. Research:***
  - **Average economic loss of $15.57/sick animal**
    - **» Only includes treatment costs and losses from decreased average daily gain**
- **Brooks et al. Research:****
  - **Decreased average daily gain of 2.5 lbs/day**
  - **Increased treatment costs of $35/head**
  - **Decreased net returns of $114/head**

Literature Cited:

*Snowder, GD, LD Van Vleck, LV Cundiff & GL Bennett. 2006. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economical factors. *J. Anim.* Sci. 84:1999-2008.

**Brooks, K, KC Raper, CE Ward, BP Holland & C Krehbiel. 2009. Economic Effects of Bovine Respiratory Disease on Feedlot Cattle during Backgrounding and Finishing Phases. Southern Agricultural Economics Association Annual Meeting, Atlanta GA.

"We started examining this flexible dose range several years ago when we had access to data that allowed us to closely look at the mortality across several thousand head of cattle. It was noticed that the bigger cattle were over-represented statistically in mortality, which was kind of contrary to what you would think. That's where the thought process behind this flex dose came from — that perhaps, on these larger cattle, the reason they were over-represented was due to under-dosing, since groups of cattle are often dosed on the average weight of the group," said Ken Blue, DVM, technical consultant for Elanco Animal Health.

FEATURES OF THE MICOTIL LABEL

- **Approved for a flexible dose range from 10 mg/kg (1.5 mL/cwt) to 20 mg/kg (3.0 mL/cwt) for both metaphylaxis and individual pull-and-treat BRD therapy**
- **Maximum injection volume of 10 mL per injection site**
- **Withdrawal time of 42 days, regardless of dose**
- **Treatment claims for *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni***
- **Micotil is indicated for the control of BRD associated with *M. haemolytica***

Dr. Thomson agrees that the research is there to show that heavier cattle routinely get under-dosed, and that the Micotil Flex Dose affords practitioners the opportunity to treat more animals at the appropriate dose relative to their weight.

"We've seen lots of studies over the years on dosage efficacy and whether or not an animal has been under-dosed. And, the last thing we want is to under-dose animals when we're trying to treat them for disease. This flexible dose of Micotil will help practitioners and producers catch more of those calves, on average, that are heavier than the load average," Thomson said.

Dr. Blue said that, in order to show the advantage of the new flexible dose, several studies were done in recent years.

"We did a pilot efficacy study (see figure 1) to get the flexible dose range approved by the FDA. We looked at negative controls in commingled cattle compared to 1.5 mL/cwt and 3.0 mL/cwt. These were high-risk cattle with some significant differences in morbidity and mortality. The key take-away with these high-risk cattle is the economics — we saw a $126 per head difference between the negative controls and the 3.0 mL/cwt. We also saw the $86 per head difference between the controls and the 1.5 mL dose. I think this study exemplifies some of the real-world situations that we see and how we can use this flexible dose to adjust our dose according to the risk of the cattle," said Blue.

Dr. Hill says the results of the Elanco trial mirror what he sees in his practice in Texas when using the flex dose.

"Depending on the time of year, we can have very different experiences with BRD. The spring is really good — as we get into the harsher weather, when there are more temperature changes from day to night, our problems get a lot worse. And, for a long time, we treated cattle based on an average load weight and we under-dosed a lot of cattle, maybe 60 percent of them. But, the flex dosing has enabled us to take care of these cattle a lot better," Hill said.

FIGURE 1: TEXAS METAPHYLAXIS STUDY RESULTS

Animal Health Data, Texas Trial[1]

	Control	Micotil 1.5 mL	Micotil 3.0 mL	P-value[2]
BRD morbidity, % (n)	34.0 (68)[a]	24.3 (97)[b]	16.8 (67)[c]	<0.01
BRD mortality, % (n)	13.5 (27)[a]	7.5 (30)[b]	6.0 (24)[b]	0.02
BRD removals, % (n)	3.5 (7)	2.5 (10)	1.5 (6)	0.33
Total BRD loss*, % (n)	17.0 (34)[a]	10.0 (40)[b]	7.5 (30)[b]	0.01
Net return/hd	-41.41[a]	45.19[b]	84.61[b]	0.02

[1]Data presented as an arithmetic means and analyzed on a pen means basis
[2]P-values are from the assessment of the overall treatment effect
*Total loss = mortality + removals
[a,b,c] Different superscripts in same row differ P<0.05

KEY POINTS

Based on a Texas study of 1,000 high-risk heifer calves sourced from multiple sale barns, Micotil metaphylaxis at 3.0 mL/cwt decreased morbidity by more than 50% when compared to nontreated controls; and more than 30% compared to Micotil at 1.5 mL/cwt.

As a result of improved health, Micotil metaphylaxis at 3.0 mL/cwt also delivered higher net returns per head at closeout:

- $126 advantage compared to nontreated controls
- $39 advantage compared to Micotil at 1.5 mL/cwt

Elanco Study No. T5C480633

Fred Reuter, DVM, who practices near El Reno, Oklahoma, agrees that treating based on the average weight of the load will leave some cattle under-dosed, and said he has taken part in some studies in the past that were further investigated to quantify this.

"When you treat cattle on the average, some of them are going to get a little extra, and some of them are not going to get what they need. So, if you allow that flex dose to come into play, you will do a more adequate job of treating the total population. We did an analysis of a previously conducted study (see figure 2) related to this. The most important thing that came out of this study was the variability of health between loads of cattle, even when they were all purchased from the same order buyers, the same sale barns, and treated exactly the same as far as a processing program except for the Micotil dosing," said Reuter.

"We saw a wide range of morbidity that occurred between these groups of cattle. We didn't have flex dose at the time we did this study, but we did the calculations to see which cattle were under-dosed and which would not have been under-dosed. These cattle were actually dosed according to their own individual weight in this trial, but you can see that if these cattle would have been dosed based on the average weight and received only the 1.5 mL dose, only 54 percent would have received the minimum dose. If we would have increased the dose to 2.0 mL, then 100 percent of the cattle would have received the minimum required dose," said Reuter.

Reuter adds that he personally sticks with the 2.0 mL dose in his practice, but in some cases he bumps up to the 3.0 mL dose.

In regards to how he communicates with his clients that Micotil Flex Dose is an effective BRD treatment, Dr. Hill says that the research demonstrates the value and helps producers make their decision easier.

BRD IMPACT ON OVERALL PERFORMANCE[1]

Research shows that as the number of antimicrobial treatments increased:

- **Cost-per-unit increased**
- **Net returns declined**
- **Marbling scores, color stability and overall consumer acceptance of the final beef product decreased**

Study results emphasize the importance of treating BRD effectively the first time to avoid expensive re-treats and a negative impact on meat quality.

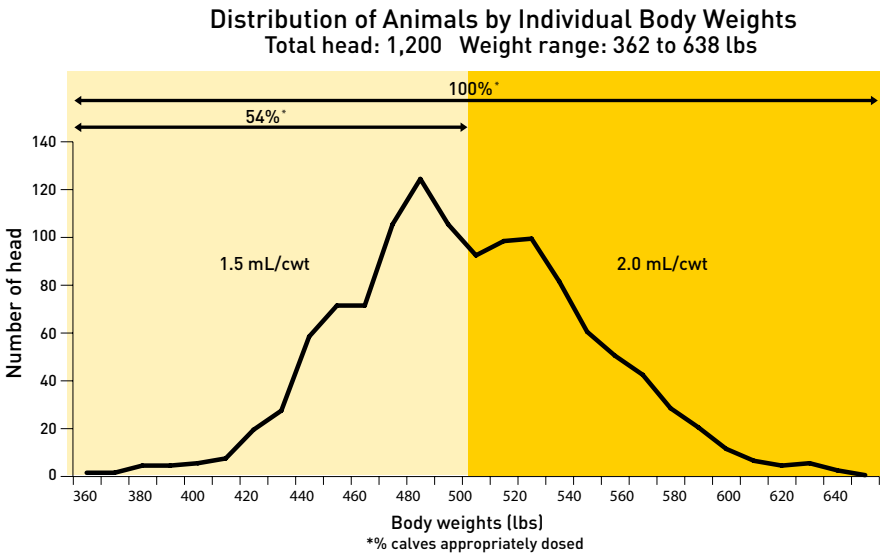
[1] Brooks, K, KC Raper, CE Ward, BP Holland & C Krehbiel. 2009. Economic Effects of Bovine Respiratory Disease on Feedlot Cattle during Backgrounding and Finishing Phases. Southern Agricultural Economics Association Annual Meeting, Atlanta GA.

"The data that's been generated by different trials over the years demonstrates the economic value of using Micotil as a metaphylactic drug. It's not a hard sell. The medication cost is significantly less than the cost of the weight loss experienced by untreated animals at the time of closeout. So, I think metaphylaxis is widely practiced because it's critical to treat these animals effectively the first time. We probably use it on 80 percent to 85 percent of our cattle or more in certain times of the year," said Hill.

Dr. Thomson agrees that, not only is treating metaphylactically cost effective, it's also a more judicious use of antibiotics.

"I'm very proud of our profession and our industry. I think we've done an outstanding job of moving forward on judicious use of antibiotics compared to when I first started in practice. I also think it's very hard to think of points in time, especially when you're talking about BRD, when a person can justify using extra-label drugs for that purpose. We have a big responsibility of helping the beef industry, helping our

FIGURE 2: ADJUSTING TREATMENT DOSAGES TO COMPENSATE FOR WEIGHT VARIATION



TRIAL DESIGN

- 14 truckloads of cattle purchased in an 11-day period
- Transportation time ranged from 4.5 hours to 12 hours
- Cattle processed within 18 hours of arrival
- 3-day evaluation period used on Micotil metaphylaxis calves
- 502-lb average arrival weight +/- 41-lb variation
- All cattle within this study were individually and accurately dosed
- However, in most production settings dosages are determined by treating to the average — which means a percentage of cattle are under-dosed
- When considering the weight variability in a truckload, the utilization of different treatment dosages allows for more cattle to receive the minimum required dose (min. of 1.5 mL/cwt)
- For example: If cattle were dosed according to the average, only 54% would receive a minimum 1.5 mL/cwt dose. By increasing the dose to 2.0 mL/cwt, then 100% of cattle would receive the minimum required dose

Elanco Study Number: T5CB39905

clients, and promoting safe, wholesome beef. And, it starts with judicious use of antibiotics in the veterinary profession," Thomson said.

Dr. Hill agrees, and says that Micotil Flex Dose is an important tool for effective BRD treatment that fits in the scope of judicious antibiotic use.

"I think the use of rogue antibiotics and the use of drugs that aren't approved for beef cattle is really on the decline. I think we're doing an excellent job and the veterinary profession and the cattle industry should be proud of what they've done. And, the flex dose has certainly given us another tool to increase our performance," said Hill.

FLEX DOSE SYRINGE REDUCES THE CHANCE OF SELF INJECTION

"Our Flex Dose safety syringe has two great points. Number one is the plastic needle guard. With that guard, when you use the proper needle length, which is 5/8 or 1/2 inch, there is no exposure to an uncovered needle. The only time that the needle is exposed is during the injection process. The needle guard also features small barbs that tent the skin, enabling one-handed use of the syringe. The second important point is that it has a double-action trigger. There's a two-stage trigger lock, and the pressure on the animal releases the trigger. This greatly reduces the chance for an accidental self injection."

- Ken Blue, DVM, Technical Consultant, Elanco Animal Health

- **12-mL, two-stage activated syringe**
- **Patented technology**
- **Withstands the most challenging environments at feedyards and stocker operations**

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.

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

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

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

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

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

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

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

Warnings:

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

Note To The Physician: The cardiovascular system is the target of toxicity and should be monitored closely. Cardiovascular toxicity may be due to calcium channel blockade. In dogs, administration of intravenous calcium offset Micotil-induced tachycardia and negative inotropy (decreased contractility). Dobutamine partially offset the negative inotropic effects induced by Micotil in dogs. 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 1-800-428-4441. Evite el contacto con los ojos.

Nota Para El Médico: El sistema cardiovascular es el blanco de la toxicidad y debe vigilarse estrechamente. La toxicidad cardiovascular puede deberse al bloqueo de los canales de calcio. En los perros, la administración intravenosa de calcio compensò la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensò 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.

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

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

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

Adverse Reactions: The following adverse reactions have been reported post-approval: In cattle: injection site swelling and inflammation, lameness, collapse, anaphylaxis/anaphylactoid reactions, decreased food and water consumption, and death. In sheep: dyspnea and death.

For a complete listing of adverse reactions for tilmicosin phosphate reported to the CVM see http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm

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

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

Effectiveness: In a multi-location field study, 1508 calves with naturally occurring BRD were treated with Micotil. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude and activity, normal respiration, and a rectal temperature of <104°F on Day 13. The cure rate was significantly higher (P=0.004) in Micotil-treated calves (63.1%) compared to saline-treated calves (29.2%). During the treatment phase of the study, there were 10 BRD-related deaths in the Micotil-treated calves compared to 47 in the saline-treated calves.

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

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

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

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

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

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

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

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

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

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

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

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

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

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*Micotil® is a trademark of Eli Lilly and Company.

Micotil® is a trademark for Elanco's brand of tilmicosin injection.
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