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NADA 140-929, Approved by FDA

PA9041DEAMP

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.

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 β-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 Subcutáneo 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)
<i>Mannheimia (Pasteurella) haemolytica</i>	3.12
<i>Pasteurella multocida</i>	6.25
<i>Histophilus somni</i>	6.25
<i>Mycoplasma dispar</i>	0.097
<i>M. bovirhinis</i>	0.024
<i>M. bovoculi</i>	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. 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.

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.

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 per 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.

CONTRAINDICATION: 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.

How Supplied: Micotil® 300 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). Proteger de la directa luz solar.

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Manufactured for:
Elanco Animal Health • A Division of Eli Lilly and Company
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