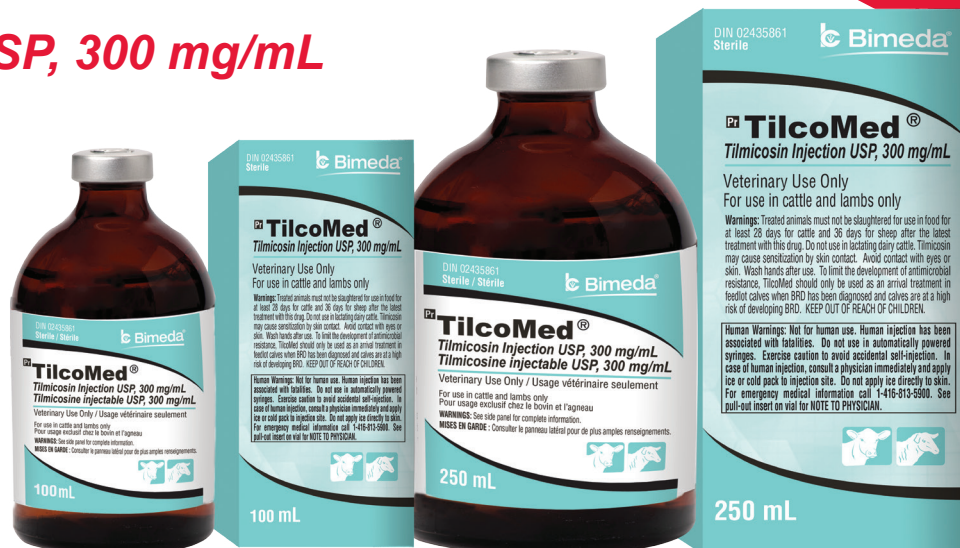


Pr TilcoMed®

Tilmicosin Injection USP, 300 mg/mL Sterile

DIN 02435861

Veterinary Use Only
For use in cattle and lambs only



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*.

DESCRIPTION

TilcoMed® is a preconstituted solution of the antibiotic tilmicosin. Each mL contains 300 mg of tilmicosin activity, 25% w/v propylene glycol, phosphoric acid for pH adjustment and water for injection q.s. Tilmicosin is produced semi-synthetically and is a member of the macrolide class of antibiotics.

PACKAGING

LIST NO.	UNIT PACKAGE	CASE SIZE
1TIL001P	100 mL	12
1TIL002P	250 mL	12

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See reverse side for Administration and Dosage.



BimedaMTC.com

TilcoMed®

Tilmicosin Injection USP, 300 mg/mL

Sterile

DIN 02435861

Veterinary Use Only

ACTIVE INGREDIENTS:

Active ingredients (per mL): 300 mg tilmicosin, USP

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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 lbs.). Do not inject more than 25 mL per injection site. If no improvement is noted within 48 hours, the diagnosis should be reconfirmed.

Note: To limit the development of antimicrobial resistance, TilcoMed should only be used as an arrival treatment when: 1) BRD has been diagnosed and 2) calves are at high risk of developing BRD. One or more of the following factors typically characterizes calves at high risk of developing BRD: commingling of calves from multiple sources; extended transport times (that may have included few if any rest stops) and excessive shrink; continued exposure to extremely wet and cold weather conditions and/or exposure to wide ambient temperature changes from origin to arrival; stressful arrival processing procedures such as castration and dehorning; recent weaning and poor vaccination status. 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.

CAUTIONS:

DO NOT ADMINISTER TO SWINE. INJECTION OF TILMICOSIN IN SWINE HAS BEEN FATAL.

WARNINGS:

Treated animals must not be slaughtered for use in food for at least 28 days for cattle and 36 days for sheep after the latest treatment with this drug. Do not use in lactating dairy cattle. Tilmicosin may cause sensitization by skin contact. Avoid contact with eyes or skin. Wash hands after use. To limit the development of antimicrobial resistance, TilcoMed should only be used as an arrival treatment in feedlot calves when BRD has been diagnosed and calves are at a high risk of developing BRD. KEEP OUT OF REACH OF CHILDREN.

HUMAN WARNINGS:

Not for human use. Human injection has been associated with fatalities. Do not use in automatically powered syringes. Exercise 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 1-416-813-5900.

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

MICROBIOLOGY:

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. One hundred thirty-four of 139 (96.4%) *Mannheimia (Pasteurella) haemolytica* isolates tested were inhibited by less than or equal to 3.12 µg/mL tilmicosin. With *Pasteurella multocida* Carter Type A of bovine origin, 53/54 (98.2%) isolates tested were inhibited by less than or equal

Microorganism	Minimum Inhibitory Concentration (µg/mL)	Microorganism	Minimum Inhibitory Concentration (µg/mL)
<i>Pasteurella multocida</i>	6.25	<i>Fusobacterium necrophorum</i>	3.12
<i>Mannheimia (Pasteurella) haemolytica</i>	3.12	<i>Escherichia coli</i>	≥ 50.00
<i>Haemophilus somnus</i>	6.25	<i>Salmonella typhimurium</i>	≥ 50.00
<i>Staphylococcus aureus</i>	0.78	<i>Mycoplasma dispar</i>	0.097
<i>Streptococcus agalactiae</i>	3.12	<i>Mycoplasma bovis</i>	0.024
<i>Actinomyces pyogenes</i>	0.024	<i>Mycoplasma bovovulii</i>	0.048
<i>Clostridium perfringens</i>	3.12	<i>Acholeplasma laidlawii</i>	0.024
<i>Clostridium sordellii</i>	3.12		

to 12.5 µg/mL tilmicosin and 39/54 (72.2%) by less than or equal to 6.25 µg/mL. 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 tilmicosin 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 tilmicosin 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 tilmicosin-induced tachycardia and negative inotropy, restoring arterial pulse

pressure within approximately 20 minutes. Dobutamine dose-dependently partially offset the negative inotropic effects induced by tilmicosin in dogs, but did not have an effect on the increased heart rate caused by tilmicosin. adrenergic antagonists, such as propranolol, exacerbated the negative inotropy of tilmicosin in dogs.

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

In swine, intramuscular injection of tilmicosin at 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 tilmicosin at 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 given 4.5 mg/kg and 5.6 mg/kg of tilmicosin 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 tilmicosin at 10, 30 and 50 mg/kg of body weight, each injected at 72 hour intervals for 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 tilmicosin group. Subcutaneous doses of tilmicosin 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 5 mg of tilmicosin/kg of body weight.

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

PHARMACOKINETICS:

A single subcutaneous injection of tilmicosin 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 below 30°C (86°F). Protect from light. Once opened, use contents within 28 days.

HOW SUPPLIED: TilcoMed® is supplied in multi-dose amber vials containing 50, 100 or 250 mL.

Imported and distributed by: Bimeda – MTC Animal Health Inc. / Santé Animale Inc., Cambridge ON N3C 2W4
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