Elanco™

THE RIGHT SOLUTION AT THE RIGHT TIME

Elanco™ Increxxa™ (tulathromycin injection)™

Baytril® 100 (enrofloxacin)

Elanco Micotil® (tilmicosin injection)™

Elanco Tylan® Injection™

Loncor™ 300 (florfenicol)

ZELNATE®

AN OVERVIEW OF ANTIBIOTICS

There's a lot of confusion out there about how antibiotics work and the likelihood of antibiotic resistance. The following information addresses this confusion and demonstrates how Elanco's portfolio offers products to effectively address BRD.

ALL ANTIBIOTICS DO NOT WORK THE SAME

Four distinct characteristics define how antibiotics work:

BACTERICIDAL ANTIBIOTICS

Kill infectious bacteria

BACTERIOSTATIC ANTIBIOTICS

Inhibit the growth of infectious bacteria

CONCENTRATION-DEPENDENT ANTIBIOTICS

Use high drug concentrations over a shorter time period to overpower infectious bacteria

TIME-DEPENDENT ANTIBIOTICS

Use low drug concentrations over a longer time period to overcome infectious bacteria

Sick cattle are often dehydrated and malnourished due to loss of appetite and may suffer from reduced lung function, all of which suppress their immune systems.

Sick cattle recover from disease when their immune systems overcome infection. Both "cidal" and "static" antibiotics assist the immune system:

- **Cidal drugs kill bacteria,** taking stress off the animal's immune system so it can work more efficiently to clear the infection.
- **Static drugs inhibit bacterial growth** by remaining in serum and tissue for a longer time period, giving the animal's immune system a chance to clear the infection.

The following table organizes commonly used antibiotics by their modes of action against BRD pathogens.

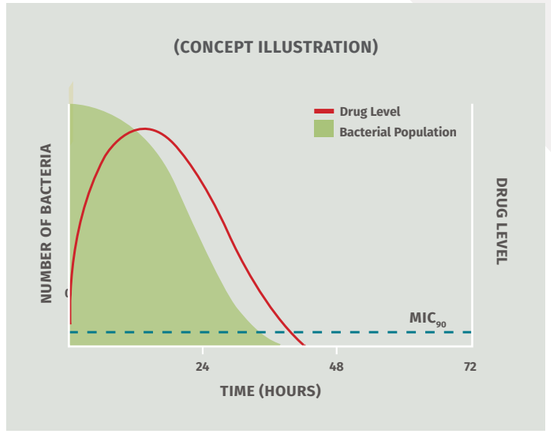
PRODUCT MODE OF ACTION CHART

	BACTERICIDAL	BACTERIOSTATIC
CONCENTRATION-DEPENDENT	• Baytril® 100 (enrofloxacin) • Advocin® (danofloxacin)	
TIME-DEPENDENT	• Nuflor® (florfenicol) Injectable Solution* • Resflor Gold® (florfenicol and flunixin meglumine) • Excede® (ceftiofur crystalline free acid) Sterile Suspension • Excenel® RTU (ceftiofur hydrochloride) Sterile Suspension • Naxcel® (ceftiofur sodium) Sterile Powder • Penicillin	• Increxxa™ (tulathromycin injection) • Micotil® (tilmicosin injection) • Draxxin® (tulathromycin) Injectable Solution • Zactran® (gamithromycin) • Zuprevo® (tildipirosin) • Nuflor® (florfenicol) Injectable Solution* • Bio-Mycin® 200 (oxytetracycline) Injection • Liquamycin® LA-200® (oxytetracycline injection)

***Nuflor has been reported to show bactericidal activity against certain bacterial strains. See Nuflor label for additional information.**

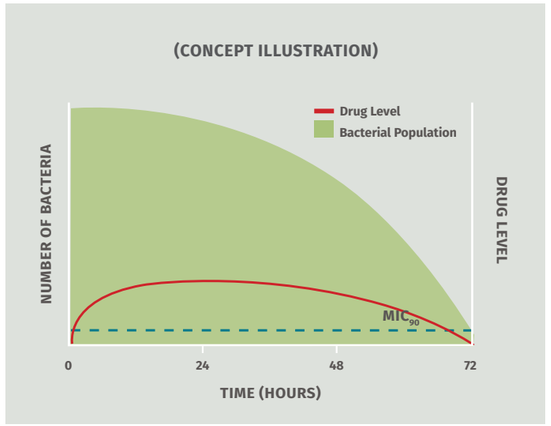
The following charts depict how concentration-dependent and time-dependent antibiotics work differently against bacteria.

FIGURE 1:
CONCENTRATION-DEPENDENT



The effectiveness of concentration-dependent drugs is dependent upon high drug levels that rapidly kill bacteria.

FIGURE 2:
TIME-DEPENDENT



Time-dependent drugs inhibit bacteria's growth over time and require drug concentrations to remain above MIC (minimum inhibitory concentration) at the site of infection for as much of the dosing interval as possible.

THE DEVELOPMENT OF ANTIBIOTIC RESISTANCE

The number of bacteria in a typical BRD-infected lung is quite large and multiplies rapidly. Within this infection, it is not unusual for small numbers of resistant, or mutant, bacteria to occur naturally.

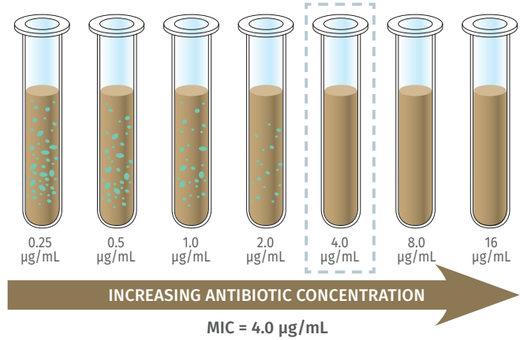
LOW DRUG CONCENTRATIONS CAN CONTRIBUTE TO ANTIBIOTIC RESISTANCE

If antibiotics are not administered in adequate concentrations, these resistant bacteria may survive while more susceptible bacteria are killed. This "selection" for the survival of resistant bacteria may result in:

- Treatment failure
- The spread of disease to pen mates
- Harder to treat relapse infections
- Death

Time-dependent antibiotics rely on maintaining the **minimum inhibitory concentration (MIC)** of a drug over time – (Fig. 2) – this is the minimum amount of drug needed to suppress replication of bacteria. This can be problematic if the animal's immune system is compromised and mutant bacteria survive to become resistant.

FIGURE 3:
DETERMINING THE MIC OF AN ANTIMICROBIAL

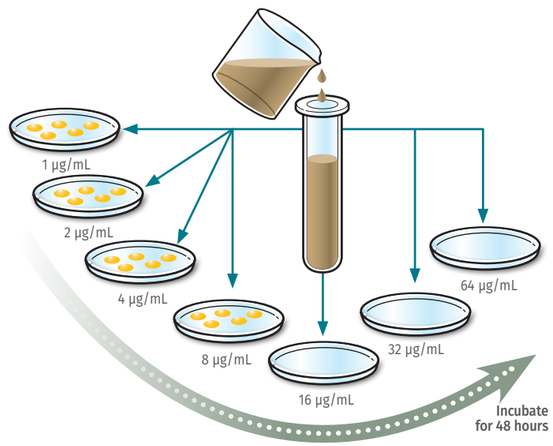


First, a bacterial inoculum is placed into each test tube, usually about 100,000 bacteria (105 cfu/mL). Bacteria then incubate for 16 to 24 hours. The tube with the lowest concentration that shows no visible growth is the MIC for that drug/bug combination.

HIGH DRUG CONCENTRATIONS CAN HELP MINIMIZE RESISTANCE

One approach to combatting antibiotic resistance is through administration of a drug that achieves the **mutant prevention concentration (MPC)** (Fig. 1). MPC is the concentration of an antibiotic needed to prevent growth of resistant mutant bacterial strains *in vitro*.* Some antibiotics can achieve and sustain MPC levels at the infection site.

FIGURE 4:
DETERMINING THE MPC OF AN ANTIBIOTIC



MPC = MIC of the most resistant mutant in a large population of bacteria

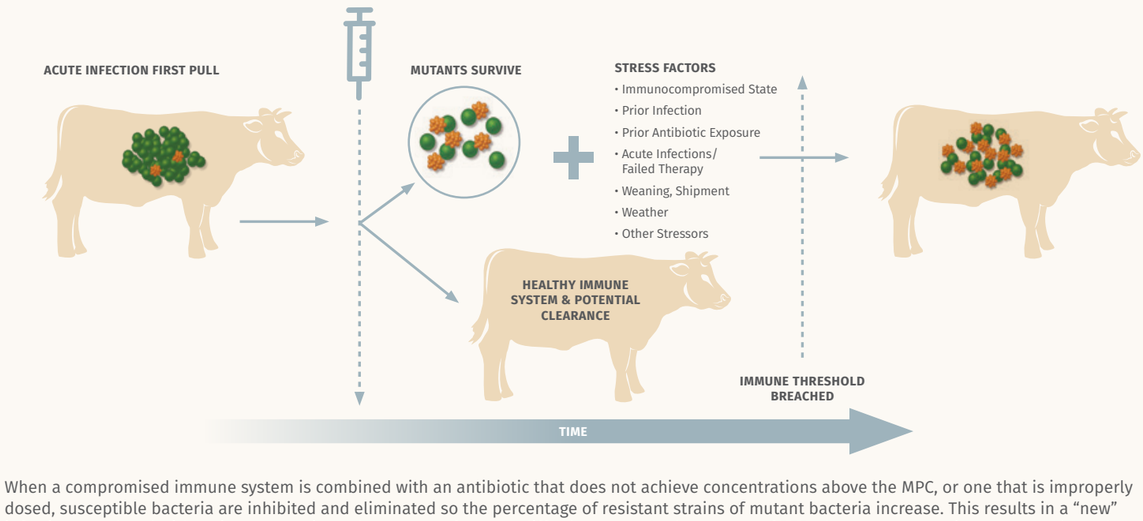
The MPC test is run by making poured agar plates with increasing concentrations of antimicrobial, starting at the MIC and going up. This is denoted by n1, n2, n3, etc. One billion to 10 billion bacteria from late-log or stationary-phase growth are then plated evenly on the surface of each plate and allowed to grow overnight. If growth occurs on a plate, then the antimicrobial concentration is less than the MIC of the most resistant mutants, or less than the MPC.

The first plate that shows no growth is the MPC of an antimicrobial concentration and equals the MIC of the most resistant mutants. The MPC concept and therefore this test is particularly important because the number of bacteria used in this test most accurately represents the level of infection of a bovine lung with acute BRD.

At therapeutic drug levels, **not all antibiotics achieve and sustain MPC.**[1] Choosing a drug that achieves MPC may help minimize the selection for antibiotic resistance during treatment.

FIGURE 5:
CONSEQUENCE OF TREATING AT MIC (CONCEPT ILLUSTRATION)

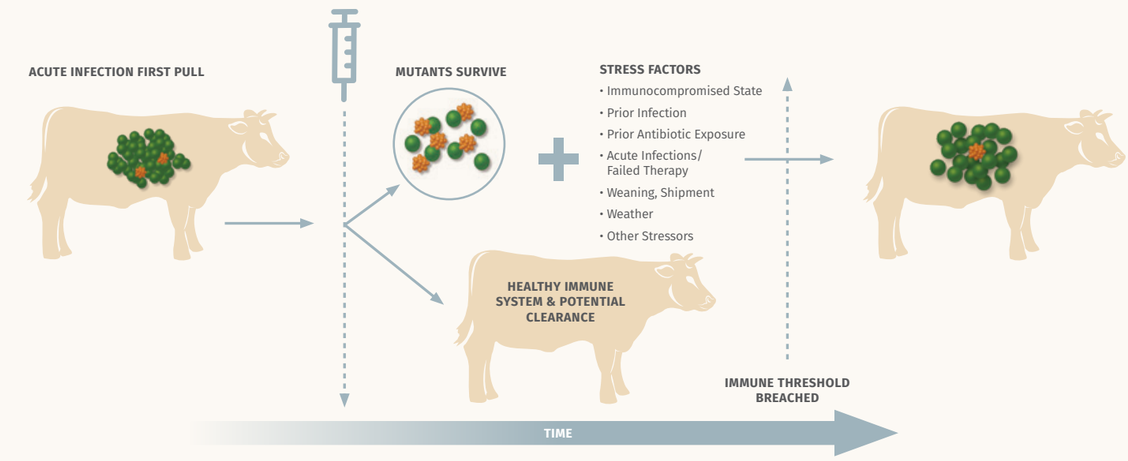
ANTIBIOTIC THERAPY – (MIC DOSAGE)



When a compromised immune system is combined with an antibiotic that does not achieve concentrations above the MPC, or one that is improperly dosed, susceptible bacteria are inhibited and eliminated so the percentage of resistant strains of mutant bacteria increase. This results in a "new" infection populated with resistant organisms that are now far more difficult to treat. In the context of BRD, these mutant strains can spread to other pen mates or even result in clinical failure from relapse infections.

FIGURE 6:
EFFECTIVE DOSING ABOVE THE MPC (CONCEPT ILLUSTRATION)

ANTIBIOTIC THERAPY – (MPC DOSAGE)



In this case, dosing over the MPC kills both susceptible and resistant subpopulations, and the immune system clears the infection. Even if the immune threshold is breached, the resident bacteria remain largely susceptible to the antimicrobial.

*The clinical significance of *in vitro* data has not been determined.

THE COST OF BRD

Bovine respiratory disease (BRD) is a big deal and a big challenge. Commonly known as shipping fever or pneumonia, BRD is one of the most important diseases in the cattle industry. It costs producers about $1 billion annually[2] due to death, reduced performance, treatment and labor. While management and vaccination are common prevention practices, antibiotics are still necessary for treatment.

BRD is caused by a broad range of pathogens and brought on by stressors, such as weather, transportation, weaning and comingling that can leave cattle vulnerable to disease. You can take the challenge of BRD and breathe easier with the Elanco BRD portfolio. With a variety of products for control and treatment, you can choose from multiple modes of action (MOA) to select the right solution to help keep cattle productive and healthy.

BREATHE EASIER WITH ELANCO'S BRD SOLUTIONS

We offer a unique anti-infective portfolio of solutions including Increxxa™ (tulathromycin injection), Micotil® (tilmicosin injection), Baytril® 100 (enrofloxacin), Loncor® 300 (florfenicol), Tylan® 200 Injection (tylosin) and Zelnate® DNA Immunostimulant giving you several options for control, treatment and immune system stimulation.

PRODUCT	ANTIBIOTIC CLASS	MOA	RECOMMENDED PROTOCOL	BOVINE TYPE
Elanco Increxxa (tulathromycin injection)	Macrolide	Tulathromycin	Metaphylaxis treatment. First-pull option.	Beef and dairy cattle.
Elanco Micotil (tilmicosin injection)	Macrolide	Tilmicosin	Metaphylaxis treatment. First-pull option. Pull-and-treat therapy.	Beef cattle and dairy calves.
Baytril 100 (enrofloxacin)	Fluoroquinolone	Enrofloxacin	Metaphylaxis treatment. First or second pull depending on modes of action previously used.	Beef and dairy cattle.
Loncor 300 (florfenicol)	Phenicols	Florfenicol	First or second pull depending on modes of action previously used.	Beef cattle and dairy calves.
Elanco Tylan Injection	Macrolide	Tylosin	Pull-and-treat option.	Beef and non-lactating dairy cattle.
ZELNATE	NA	Immunostimulant	Administer during or within 24 hours of a perceived stressful event.	Cattle 4 months of age or older.

GET TO KNOW YOUR OPTIONS

With more than 40 years of BRD technical experience, we have a long heritage of and commitment to continually researching and improving our portfolio with innovative treatments. Our dedication to antibiotic stewardship also ensures you have access to different modes of action and the right products to treat the right diseases. Each solution is backed with quality manufacturing and on-site consultations with the Elanco technical team to develop the right solutions for any operation.

CONSULT YOUR VETERINARIAN TO DETERMINE WHICH ELANCO PRODUCTS ARE RIGHT FOR YOUR BRD PROTOCOL.

Baytril® 100
(enrofloxacin)

100 mg/mL Antimicrobial Injectable Solution
For Subcutaneous Use In Beef Cattle And Non-Lactating Dairy Cattle
For Intramuscular Or Subcutaneous Use In Swine
Not For Use In Female Dairy Cattle 20 Months Of Age Or Older
Or In Calves To Be Processed For Veal

CAUTION:
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
Federal (U.S.A.) law prohibits the extra-label use of this drug in food-producing animals.
To assure responsible antimicrobial drug use, enrofloxacin should only be used as a second-line drug for colibacillosis in swine following consideration of other therapeutic options.

PRODUCT DESCRIPTION:
Baytril® 100 is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broad-spectrum fluoroquinolone antimicrobial agent.
Each mL of Baytril® 100 contains 100 mg of enrofloxacin. Excipients are L-arginine base 200 mg, n-butyl alcohol 30 mg, benzyl alcohol (as a preservative) 20 mg and water for injection q.s.

CHEMICAL NOMENCLATURE AND STRUCTURE:
1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

INDICATIONS:
Cattle - Single-Dose Therapy: Baytril® 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica, P. multocida, H. somni* and *M. bovis*.
Cattle - Multiple-Day Therapy: Baytril® 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* in beef and non-lactating dairy cattle.
Swine: Baytril® 100 is indicated for the treatment and control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, Streptococcus suis, Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*. Baytril® 100 is indicated for the control of colibacillosis in groups or pens of weaned pigs where colibacillosis associated with *Escherichia coli* has been diagnosed.

DOSAGE AND ADMINISTRATION:
Baytril® 100 provides flexible dosages and durations of therapy.
Baytril® 100 may be administered as a single dose for one day for treatment and control of BRD (cattle), for treatment and control of SRD or for control of colibacillosis (swine), or for multiple days for BRD treatment (cattle). Selection of the appropriate dose and duration of therapy for BRD treatment in cattle should be based on an assessment of the severity of the disease, pathogen susceptibility and clinical response.
Cattle:
Single-Dose Therapy (BRD Treatment): Administer, by subcutaneous injection, a single dose of 7.5-12.5 mg/kg of body weight (3.4-5.7 mL/100 lb).
Multiple-Day Therapy (BRD Treatment): Administer daily, a subcutaneous dose of 2.5-5 mg/kg of body weight (1.1-2.3 mL/100 lb).
Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.
Single-Dose Therapy (BRD Control): Administer, by subcutaneous injection, a single dose of 7.5 mg/kg of body weight (3.4 mL/100 lb).
Examples of conditions that may contribute to calves being at high risk of developing BRD include, but are not limited to, the following:
- Transportation with animals from two or more farm origins.
- An extended transport time with few to no rest stops.
- An environmental temperature change of ≥30°F during transportation.
- A ≥30°F range in temperature fluctuation within a 24-hour period.
- Exposure to wet or cold weather conditions.
- Excessive shrink (more than would be expected with a normal load of cattle).
- Stressful arrival processing procedures (e.g., castration or dehorning).
- Exposure within the prior 72 hours to animals showing clinical signs of BRD.

Administered dose volume should not exceed 20 mL per injection site.

Table 1 – Baytril® 100 Dose and Treatment Schedule for Cattle*

Weight (lb)	Treatment: Single-Dose Therapy 7.5 - 12.5 mg/kg Dose Volume (mL)	Treatment: Multiple-Day Therapy 2.5 - 5.0 mg/kg Dose Volume (mL)	Control: Single-Dose Therapy 7.5 mg/kg Dose Volume (mL)
100	3.5 - 5.5	1.5 - 2.0	3.5
200	7.0 - 11.0	2.5 - 4.5	7.0
300	10.5 - 17.0	3.5 - 6.5	10.5
400	14.0 - 22.5	4.5 - 9.0	14.0
500	17.0 - 28.5	5.5 - 11.5	17.0
600	20.5 - 34.0	7.0 - 13.5	20.5
700	24.0 - 39.5	8.0 - 16.0	24.0
800	27.5 - 45.5	9.0 - 18.0	27.5
900	31.0 - 51.0	10.0 - 20.5	31.0
1000	34.0 - 57.0	11.0 - 23.0	34.0
1100	37.5 - 62.5	12.5 - 25.0	37.5

*Dose volumes have been rounded to the nearest 0.5 mL within the dose range.
Swine:
Administer, either by intramuscular or subcutaneous (behind the ear) injection, a single dose of 7.5 mg/kg of body weight (3.4 mL/100 lb). Administered dose volume should not exceed 5 mL per injection site.
For the control of colibacillosis, administration should be initiated within the first 60 days post-weaning when clinical signs are present in at least 2% of the animals in the group. If no improvement is noted within 48 hours, the diagnosis should be reevaluated.

Table 2 – Baytril® 100 Dose Schedule for Swine

Weight (lb)	Dose Volume (mL)
15	0.5
30	1.0
50	1.7
100	3.4
150	5.1
200	6.8
250	8.5

Dilution of Baytril® 100: Baytril® 100 may be diluted with sterile water prior to injection. The diluted product should be used within 24 hours. Store diluted solution in amber glass bottles between 4-40°C (36-104°F).

Table 3 – Dilution Schedule*

Swine Weight	mL of Baytril® 100	mL of sterile water	Number of doses
10 lb	34 mL	66 mL	100
15 lb	51 mL	49 mL	100
20 lb	68 mL	32 mL	100
25 lb	85 mL	15 mL	100

*For 1 mL dose volume from diluted solution

Use within 30 days of first puncture and puncture a maximum of 30 times with a needle or 4 times with a dosage delivery device. Any product remaining beyond these parameters should be discarded.

RESIDUE WARNINGS:
Cattle: Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. This product is not approved for female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. **Swine:** Animals intended for human consumption must not be slaughtered within 5 days of receiving a single-injection dose.

HUMAN WARNINGS:
Not for use in humans. Keep out of reach of children. Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. For customer service or to obtain product information, including a Safety Data Sheet, call 1-800-633-3796. For medical emergencies or to report adverse reactions, call 1-800-422-9874.

PRECAUTIONS:
The effects of enrofloxacin on cattle or swine reproductive performance, pregnancy and lactation have not been adequately determined. The long-term effects on articular joint cartilage have not been determined in pigs above market weight.
Subcutaneous injection in cattle and swine, or intramuscular injection in swine, can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.
Baytril® 100 contains different excipients than other Baytril® products. The safety and efficacy of this formulation in species other than cattle and swine have not been determined.
Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures. Quinolone-class drugs have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. See Animal Safety section for additional information.

ADVERSE REACTIONS:
No adverse reactions were observed during clinical trials.
For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

MICROBIOLOGY:
Enrofloxacin is bactericidal and exerts its antibacterial effect by inhibiting bacterial DNA gyrase (a type II topoisomerase) thereby preventing DNA supercoiling and replication which leads to cell death.[1] Enrofloxacin is active against Gram-negative and Gram-positive bacteria.

EFFECTIVENESS:
Cattle: A total of 845 calves with naturally-occurring BRD were treated with Baytril® 100 in eight field trials located in five cattle-feeding states. Response to treatment was compared to non-treated controls. Single-dose and multiple-day therapy regimens were evaluated. BRD and mortality were significantly reduced in enrofloxacin-treated calves. No adverse reactions were reported in treated animals.
The effectiveness of Baytril® 100 for the control of respiratory disease in cattle at high risk of developing BRD was evaluated in a six-location study in the U.S. and Canada. A total of 1,150 crossbred beef calves at high risk of developing BRD were enrolled in the study. Baytril® 100 (7.5 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within two days after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for success on Day 14 post-treatment. Treatment success in the Baytril® 100 group (497/573, 87.83%) was significantly higher (P = 0.0013) than success in the saline control group (455/571, 80.92%). In addition, there were more treatment successes (n = 13) than failures (n = 3) in the group of animals positive for *M. bovis* on Day 0 that were treated with Baytril® 100. No product-related adverse reactions were reported.
Swine: A total of 590 pigs were treated with Baytril® 100 or saline in two separate natural infection SRD field trials. For the treatment of SRD, the success rate of enrofloxacin-treated pigs that were defined as "sick and febrile" (increased respiratory rate, labored or dyspneic breathing, depressed attitude and a rectal temperature ≥ 104°F) was statistically significantly greater than the success rate of saline-treated "sick and febrile" pigs. For the control of SRD, mean rectal temperature, mortality (one trial) and morbidity were statistically significantly lower for enrofloxacin-treated pigs in pens containing a percentage of "sick and febrile" pigs compared to saline-treated pigs.
The effectiveness of Baytril® 100 administered as a single SC dose of 7.5 mg/kg BW for the treatment and control of SRD associated with *M. hyopneumoniae* was demonstrated using an induced infection model study and three single-site natural infection field studies. In the model study, 72 healthy pigs were challenged with a representative *M. hyopneumoniae* isolate and treated with Baytril® 100 or saline. A statistically significant (P < 0.0001) decrease in the mean total lung lesion score was observed in the Baytril® 100-treated group (4%) compared with the saline-treated group (27%) at 10 days post-treatment.
In two field studies evaluating effectiveness for treatment of SRD, a total of 300 pigs with clinical signs of SRD (moderate depression, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) were enrolled and treated with Baytril® 100 or saline. At 7 days post-treatment, the cure rate was statistically significantly higher at each site (P < 0.0001) in the Baytril® 100-treated groups (61.3% and 92%) compared with the saline-treated groups (26.7% and 33.3%). In one field study evaluating effectiveness for control of SRD, a group of 400 pigs in which > 15% had clinical signs of SRD (moderate depression score, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) was enrolled and treated with Baytril® 100 or saline. At 7 days post-treatment, the cure rate was statistically significantly higher (P < 0.0002) in the Baytril® 100-treated group (70.0%) compared with the saline-treated group (48.5%). In addition to *M. hyopneumoniae, B. bronchiseptica* was also isolated in sufficient numbers from these field studies to be included in the SRD treatment and control indications.
The effectiveness of Baytril® 100 for the control of colibacillosis associated with *E. coli* was evaluated in a multi-site natural infection field study. At each site, when at least 5% of the pigs were defined as "clinically affected" (presence of diarrhea and either depression or gaunt/ness), all pigs were administered Baytril® 100 as a single IM dose of 7.5 mg/kg BW or an equivalent dose volume of saline. At 7 days post-treatment, the success rate was statistically significantly higher (P = 0.0350) in the Baytril® 100-treated group (61.5%) compared with the saline-treated group (44.7%).
The effectiveness of Baytril® 100 administered as a single IM dose of 7.5 mg/kg BW for the treatment and control of SRD or as a single SC dose of 7.5 mg/kg BW for the control of colibacillosis was confirmed by demonstrating comparable serum enrofloxacin concentrations following IM or SC injection into the neck of healthy male and female pigs.

TOXICOLOGY:
The oral LD50 for laboratory rats was greater than 5000 mg/kg of body weight. Ninety-day feeding studies in dogs and rats revealed no observable adverse effects at treatment rates of 3 and 40 mg/kg respectively. Chronic studies in rats and mice revealed no observable adverse effects at 5.3 and 323 mg/kg respectively. There was no evidence of carcinogenic effect in laboratory animal models. A two-generation rat reproduction study revealed no effect with 10 mg/kg treatments. No teratogenic effects were observed in rabbits at doses of 25 mg/kg or in rats at 50 mg/kg.

ANIMAL SAFETY:
Cattle: Safety studies were conducted in feeder calves using single doses of 5, 15 and 25 mg/kg for 15 consecutive days and 50 mg/kg for 5 consecutive days. No clinical signs of toxicity were observed when a dose of 5 mg/kg was administered for 15 days. Clinical signs of depression, incoordination and muscle fasciculation were observed in calves when doses of 15 or 25 mg/kg were administered for 10 to 15 days. Clinical signs of depression, inappetance and incoordination were observed when a dose of 50 mg/kg was administered for 3 days. No drug-related abnormalities in clinical pathology parameters were identified. No articular cartilage lesions were observed after examination of stifle joints from animals administered 25 mg/kg for 15 days.
A safety study was conducted in 23-day-old calves using doses of 5, 15 and 25 mg/kg for 15 consecutive days. No clinical signs of toxicity or changes in clinical pathology parameters were observed. No articular cartilage lesions were observed in the stifle joints at any dose level at 2 days and 9 days following 15 days of drug administration.
An injection site study conducted in feeder calves demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue and underlying muscle. No painful responses to administration were observed.
Swine: Subcutaneous Safety: A safety study was conducted in 32 pigs weighing approximately 57 kg (125 lb) using single doses of 5, 15 or 25 mg/kg daily for 15 consecutive days. Incidental lameness of short duration was observed in all groups, including the saline-treated controls. Musculoskeletal stiffness was observed following the 15 and 25 mg/kg treatments with clinical signs appearing during the second week of treatment. Clinical signs of lameness improved after treatment ceased and most animals were clinically normal at necropsy.
A second study was conducted in two pigs weighing approximately 23 kg (50 lb), treated with 50 mg/kg for 5 consecutive days. There were no clinical signs of toxicity or pathological changes.
An injection site study conducted in pigs demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue. No painful responses to administration were observed.
Intramuscular Safety: A safety study was conducted in 48 weaned, 20- to 22-day-old pigs. Pigs were administered Baytril® 100, at 7.5, 22.5 and 37.5 mg/kg BW by IM injection into the neck once weekly for 3 consecutive weeks. All pigs remained clinically normal throughout the study. Transient decreases in feed and water consumption were observed after each treatment. Mild, transient, post-treatment injection site swellings were observed in pigs receiving the 37.5 mg/kg BW dose. Injection site inflammation was found on post-mortem examination in all enrofloxacin-treated groups.

STORAGE CONDITIONS: Protect from direct sunlight. Do not refrigerate or freeze. Store at 20-30°C (68-86°F), excursions permitted up to 40°C (104°F). Precipitation may occur due to cold temperature. To redissolve, warm and then shake the vial.

HOW SUPPLIED:
Baytril® 100.
100 mg/mL 100 mL Bottle
100 mg/mL 250 mL Bottle
100 mg/mL 500 mL Bottle

REFERENCES:
1. Hooper, D. C., Wolfson, J. S., Quinolone Antimicrobial Agents, 2nd ed, 59 - 75, 1993.
For customer service or to obtain product information, including a Safety Data Sheet, call 1-800-633-3796.
For medical emergencies or to report adverse reactions, call 1-800-422-9874.
V-04/2016

NADA 141-068, Approved by FDA
Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201 U.S.A.
Made in Germany FLM081720

Bayer

Elanco™ AH0230

Micotil™ 300

250 mL

(tilmicosin injection)

300 mg tilmicosin, USP as tilmicosin phosphate per mL

For Use in Cattle and Sheep Only
Solo Para Uso en Bovinos y Ovinos
Do Not Use in Automatically Powered Syringes.
No Administrar con Jeringas Accionadas Automáticamente.
Approved by FDA under NADA # 140-929

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. Do not use in lambs less than 15 kg body weight. 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.

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-antienergic 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 compensó la taquicardia y los efectos inotrópicos negativos (reducción de la contractilidad) inducidos por Micotil. La dobutamina compensó 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 Subcutáneo 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 additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

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 10 mg/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 dose 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 resulted in mortality in 3 of 4 pigs, and 30 mg/kg body weight caused the death of all 4 pigs tested. Injection of 4.5 and 5.6 mg/kg body weight 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 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). Proteger de la luz solar directa.
To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

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

Manufactured for: **Elanco US, Inc.**
Greenfield, IN 46140, USA

Revised: March 2020

Elanco™ Micotil® Tilmicosin Injection ™

Elanco™ Increxxa™ (tulathromycin injection) ™

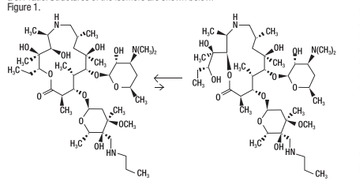
FULL PRESCRIBING INFORMATION FOR USE IN CATTLE ONLY

Elanco™ Increxxa™ (tulathromycin injection)

Injectable Solution

Antibiotic
100 mg of tulathromycin/mL
For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves), veal calves, and swine. Not for use in female dairy cattle 20 months of age or older.
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
Increxxa Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of Increxxa contains 100 mg of tulathromycin, 500 mg propylene glycol, 19.2 mg citric acid and 5 mg monothioglycerol. Sodium hydroxide or hydrochloric acid may be added to adjust pH. Increxxa consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio. Structures of the isomers are shown below.
Figure 1.



The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino) methyl]-α-L-ribo-hexopyranosyl]oxy]-2-ethyl-3,4,10- trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl- 3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-syl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Beef and Non-Lactating Dairy Cattle
BRD – Increxxa Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*; and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*.
IBK – Increxxa Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.
Foot Rot – Increxxa Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.

Suckling Calves, Dairy Calves, and Veal Calves
BRD – Increxxa Injectable Solution is indicated for the treatment of BRD associated with *M. haemolytica, P. multocida, H. somni*, and *M. bovis*.

DOSAGE AND ADMINISTRATION

Cattle
Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lb) body weight (BW). Do not inject more than 10 mL per injection site.
Table 1. Increxxa Cattle Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
100	1.1
200	2.3
300	3.4
400	4.5
500	5.7
600	6.8
700	8.0
800	9.1
900	10.2
1000	11.4

CONTRAINDICATIONS
The use of Increxxa Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS
FOR USE IN ANIMALS ONLY.
NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.
NOT FOR USE IN CHICKENS OR TURKEYS.

RESIDUE WARNINGS
Cattle
Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows.

PRECAUTIONS
Cattle
The effects of Increxxa on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS
Cattle
In one BRD field study, two calves treated with tulathromycin injection at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

POST APPROVAL EXPERIENCE
The following adverse events are based on post approval adverse drug experience reporting. Not all adverse events are reported to the FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lungs as compared to the plasma.
The extent to which lung concentrations represent free (active) drug was not examined. Therefore, the clinical relevance of these elevated lung concentrations is undetermined. Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity. Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration. Of the two variables, concentration and exposure time, drug concentration tends to be the most powerful determinant of the duration of PAE. Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.

[1] *Carbon, C. 1998. Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis., 27:28-32.*
[2] *Nightingale, C.J. 1997. Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J., 16:438–443.*

Cattle
Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 15 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tulathromycin distributes extensively into body tissues, as evidenced by volume of distribution values of approximately 11 L/kg in healthy ruminating calves.[3] This extensive volume of distribution is largely responsible for the long elimination half-life of this compound [approximately 2.75 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 8.75 days for total lung concentrations (based on data from healthy animals)]. Linear pharmacokinetics are observed with subcutaneous doses ranging from 1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.

[3] *Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.*

MICROBIOLOGY
Cattle
Tulathromycin has demonstrated *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis*, four pathogens associated with BRD; against *Moraxella bovis* associated with IBK; and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot. The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A2). The MICs against foot rot pathogens were also determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 9:1 isomer ratio of this compound.
BRD - The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders, and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.
IBK - The MICs of tulathromycin were determined for *Moraxella bovis* isolates obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from pre-treatment conjunctival swabs of calves with clinical signs of IBK enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.
Foot Rot - The MICs of tulathromycin were determined for *Fusobacterium necrophorum* and *Porphyromonas levii* obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from pre-treatment interdigital biopsies and swabs of cattle with clinical signs of foot rot enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.
Table 3. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD and IBK in the U.S. and from foot rot field studies in the U.S. and Canada.

Indicated pathogen	Date isolated	No. of isolates	MIC_{50} ** (µg/mL)	MIC_{90} ** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1999	642	2	2	0.5 to 64
Pasteurella multocida	1999	221	0.5	1	0.25 to 64
Histophilus somni	1999	36	4	4	1 to 4
Mycoplasma bovis	1999	43	0.125	1	≤ 0.063 to > 64
Moraxella bovis	2004	55	0.5	0.5	0.25 to 1
Fusobacterium necrophorum	2007	116	2	64	≤ 0.25 to > 128
Porphyromonas levii	2007	103	8	128	≤ 0.25 to > 128

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

EFFECTIVENESS
Cattle
BRD – In a multi-location field study, 314 calves with naturally occurring BRD were treated with tulathromycin injection. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. The cure rate was significantly higher (P ≤ 0.05) in tulathromycin injection-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the tulathromycin injection-treated calves compared to nine BRD-related deaths in the saline-treated calves. Fifty-two tulathromycin injection-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 tulathromycin injection-treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.
A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with tulathromycin injection to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with tulathromycin injection. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of tulathromycin injection in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves.
As a result, tulathromycin injection is considered effective for the treatment of BRD associated with *M. haemolytica, P. multocida, H. somni*, and *M. bovis* in suckling calves, dairy calves, and veal calves.
In another multi-location field study with 399 calves at high risk of developing BRD, administration of tulathromycin injection resulted in a significantly reduced incidence of BRD (11%) compared to saline-treated calves (59%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of ≤ 104°F on Day 14. There were no BRD-related deaths in the tulathromycin injection-treated calves compared to two BRD-related deaths in the saline-treated calves.
Fifty saline-treated calves classified as non-responders in this study had *Mycoplasma bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue.
Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either tulathromycin injection (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the tulathromycin injection-treated calves compared with saline-treated calves (11.3% vs. 28.9%, P = 0.0001 and 15.0% vs. 30.7%, P < 0.0001).
IBK – Two field studies were conducted evaluating tulathromycin injection for the treatment of IBK associated with *Moraxella bovis* in 200 naturally-infected calves. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of IBK and no corneal ulcer, assessed on Days 5, 9, 13, 17, and 21. Time to improvement, defined as the first day on which a calf had no clinical signs of IBK in both eyes, provided that those scores were maintained at the next day of observation, was assessed as a secondary variable. At all time points, in both studies, the cure rate was significantly higher (P < 0.05) for tulathromycin injection-treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less (P < 0.0001) in both studies for tulathromycin injection-treated calves compared to saline-treated calves.
Foot Rot - The effectiveness of tulathromycin injection for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of tulathromycin injection (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, the treatment success percentage was statistically significantly higher in tulathromycin injection-treated calves compared with saline-treated calves (60% vs. 8%, P < 0.0001 and 83.3% vs. 50%, P = 0.0088).

ANIMAL SAFETY
Cattle
Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically. An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15 mg/kg BW.
A safety study was conducted in preruminant calves 13 to 27 days of age receiving 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.

STORAGE CONDITIONS
Store below 25°C (77°F), with excursions up to 40°C (104°F).
100 mL: Use within 2 months of first puncture and puncture a maximum of 67 times. If more than 67 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.
250 mL: Use within 2 months of first puncture and puncture a maximum of 100 times. If more than 100 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16 gauge, discard any product remaining in the vial immediately after use.

HOW SUPPLIED
Increxxa (tulathromycin injection) Injectable Solution is available in the following package sizes:
100 mL vial
250 mL vial
500 mL vial
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Elanco at 1-800-422-9874. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.
Approved by FDA under ANADA # 200-666
Product of China.
Manufactured by: Elanco US Inc, Shawnee, KS 66216

October, 2020

TAKE TIME
OBSERVE LABEL DIRECTIONS
Elanco™

90198370 LV2011

ANADA 200-582, Approved by FDA

Loncor™ 300

(florfenicol)

300 mg/mL Injectable Solution

For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only
Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal

CAUTION
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
LONCOR™ 300 (florfenicol) 300 mg/mL Injectable Solution is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile LONCOR™ 300 contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol qs.

INDICATIONS
LONCOR™ 300 is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.* Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni.*

DOSAGE AND ADMINISTRATION
For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): Loncor™ 300 should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, Loncor™ 300 can be administered by a single subcutaneous (SC) injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high risk of developing BRD: LONCOR™ 300 should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

Loncor™ 300 DOSAGE GUIDE

ANIMAL WEIGHT (lbs)	IM LONCOR 300 DOSAGE 3.0 mL/100 lb Body Weight (mL)	SC LONCOR 300 DOSAGE 6.0 mL/100 lb Body Weight (mL)
100	3.0	6.0
200	6.0	12.0
300	9.0	18.0
400	12.0	24.0
500	15.0	30.0
600	18.0	36.0
700	21.0	42.0
800	24.0	48.0
900	27.0	54.0
1000	30.0	60.0

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

RECOMMENDED INJECTION LOCATION

Do not inject more than 10 mL per injection site.

CONTRAINDICATIONS
Do not use in animals that have shown hypersensitivity to florfenicol.

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.
This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. For customer service, adverse effects reporting, and/or a copy of the MSDS, call 1-800-422-9874.

PRECAUTIONS
Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Toxicity studies in dogs, rats, and mice have associated the use of florfenicol with testicular degeneration and atrophy. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

RESIDUE WARNINGS
Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. This product is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or calves born to these cows.A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

ADVERSE REACTIONS
Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

CLINICAL PHARMACOLOGY
The pharmacokinetic disposition of florfenicol was evaluated in feeder calves following single intramuscular (IM) administration at the recommended dose of 20 mg/kg body weight. Florfenicol was also administered intravenously (IV) to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability[1] (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol Following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C_{max} (µg/mL)	3.07*	1.43 - 5.60
T_{max} (hr)	3.33	0.75 - 8.00
T 1/2 (hr)	18.3**	8.30 - 44.0
AUC (µg•min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd_{ss} (L/kg)***	0.77	0.68 - 0.85
Cl (mL/min/kg)***	3.75	3.17 - 4.31

* harmonic mean
** mean value
*** following IV administration
C_{max} Maximum serum concentration
T_{max} Time at which C_{max} is observed
T 1/2 Biological half-life
AUC Area under the curve
Vd_{ss} Volume of distribution at steady state
Cl Total body clearance

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively.

MICROBIOLOGY
Florfenicol is a synthetic, broad-spectrum antibiotic active against many Gram-negative and Gram-positive bacteria isolated from domestic animals. It acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. Florfenicol is generally considered a bacteriostatic drug, but exhibits bactericidal activity against certain bacterial species. *In vitro* studies demonstrate that florfenicol is active against the bovine respiratory disease (BRD) pathogens *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* and that florfenicol exhibits bactericidal activity against strains of *M. haemolytica* and *H. somni.* Clinical studies confirm the efficacy of florfenicol against BRD as well as against commonly isolated bacterial pathogens in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

TABLE 2. Florfenicol Minimum Inhibitory Concentration (MIC) Values* of Indicated Pathogens Isolated From Natural Infections of Cattle.

Indicated pathogens	Year of isolation	Isolate Numbers	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)
Mannheimia haemolytica	1990 to 1993	398	0.5	1
Pasteurella multocida	1990 to 1993	350	0.5	0.5
Histophilus somni	1990 to 1993	66	0.25	0.5
Fusobacterium necrophorum	1973 to 1997	33	0.25	0.25
Bacteroides melaninogenicus	1973 to 1997	20	0.25	0.25

* The correlation between the *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

ANIMAL SAFETY
A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group. Decreased feed and water consumption, body weight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.

A 43-day controlled study was conducted in healthy cattle to evaluate effects of florfenicol administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, florfenicol administration had no long-term effect on body weight, rate of gain, or feed consumption.

STORAGE INFORMATION
Store below 30°C (86°F).
Stopper should not be punctured more than 90 times.
Once opened, use contents within 6 months.
The solution is light yellow to straw colored. Color does not affect potency.

HOW SUPPLIED
Loncor™ 300 is packaged in 250 mL and 500 mL glass sterile multiple-dose vials.

REFERENCE
1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. *J Vet Pharmacol Therap.* 1994; 17:253-258.

Bayer HealthCare LLC
Animal Health Division
Shawnee Mission, Kansas 66201 U.S.A.

Made in China

Bayer

DNA Immunostimulant

ZELNATE™

For Intramuscular Administration to Cattle

FOR VETERINARY USE ONLY 02293

READ IN FULL

DESCRIPTION
ZELNATE™ is a bacterial-produced plasmid DNA with a liposome carrier that stimulates the innate immune system in cattle. The innate immune system has been shown to provide a potent, rapid, nonspecific, protective response to infectious agents, such as those that can lead to Bovine Respiratory Disease (BRD). BRD is a serious condition that commonly causes lung lesions, reduced lung capacity and mortality.

The freeze-dried (desiccate) product is packaged with two different sterile diluents. The First Sterile Rehydrator (vial 1) is used to reconstitute the desiccate cake (vial 2), and then transferred to the Final Sterile Solution (vial 3) to achieve the proper concentration for administration.

INDICATION
ZELNATE™ is indicated for use as an aid in the treatment of Bovine Respiratory Disease due to *Mannheimia haemolytica* in cattle 4 months of age or older, when administered at the time of, or within 24 hours after, a perceived stressful event.

IMPORTANT STORAGE CONDITIONS
Store Refrigerated
2°C to 8°C (35°F to 46°F)
DO NOT FREEZE.

STUDY DATA
In Study A, 3- to 4-month-old steers were randomly allocated to receive either ZELNATE™ or a negative control (N=32 per group). On Day 0, each group of healthy calves was intramuscularly administered their respective treatment and challenged (intratracheally) with *Mannheimia haemolytica.* Lung lesion scores were obtained on Day 5. ZELNATE™ significantly ($p<0.05$) reduced lung lesion scores compared to the control group (Figure A).[1]

In Study B, 3- to 4-month-old steers were randomly allocated to receive either ZELNATE™ or a negative control (N=40 per group). On Day 0, each group was challenged (intratracheally) with *Mannheimia haemolytica.* Twenty four hours post-challenge (i.e., Day 1), BRD morbidity was observed to be 67.5%. At this time, each group was intramuscularly administered their respective treatment (i.e., in the face of clinical BRD). Lung lesion scores were obtained on Day 5. Among calves that lived until Day 5, ZELNATE™ numerically reduced lung lesion scores compared to the control group (data not shown). The cumulative incidence of death, associated with BRD, was 11.3%. The lung lesion scores among dead calves and those living to Day 5 were observed to be 55.3% and 17.6%, respectively. ZELNATE™ significantly ($p<0.05$) reduced mortality compared to the control group (Figure B).[2]

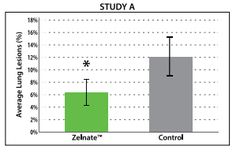


Figure A: Average lung lesion scores between calves receiving either ZELNATE™ or a negative control at the same time as an intratracheal *Mannheimia haemolytica* challenge. Lung lesion scores reflect those observed on Day 5 post-challenge.

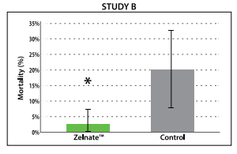


Figure B: Cumulative incidence of mortality between calves receiving either ZELNATE™ or a negative control 24 hours after an intratracheal *Mannheimia haemolytica* challenge. Mortality estimates reflect those observed from the Day of challenge (Day 0) to Day 5 post-challenge.

* = statistically significant reduction ($p<0.05$)

In conclusion, ZELNATE™, as a stand-alone therapy, has been shown to: 1) significantly reduce lung lesion scores associated with BRD when administered in the face of disease challenge (Study A), and 2) significantly reduce the risk of mortality when administered in the face of clinical BRD (Study B).

[1]Data on file. Bayer HealthCare Animal Health.
[2]Data on file. Bayer HealthCare Animal Health.

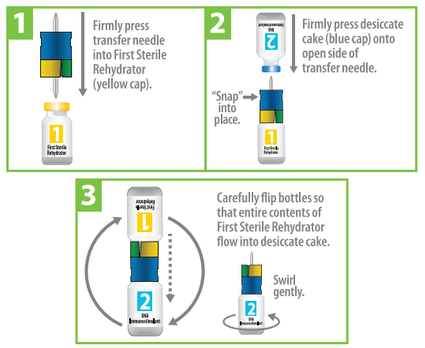
METHOD OF ADMINISTRATION
Inject 2 mL intramuscularly at the time of, or within 24 hours after, a perceived stressful event (for example: weaning, shipping, commingling or adverse environmental conditions). Use entire contents of vial once first opened.

PRECAUTION
Do not administer within 21 days of slaughter.

OTHER INFORMATION
Contains no antibiotics and no preservatives.
ZELNATE™ has shown no detectable lesions at the site of intramuscular injection.

HOW SUPPLIED
Vials of 5, 10 and 50 doses.

Mixing process must be completed in the appropriate order. Transfer needle must be fully inserted to prevent spillage.



ZELNATE™ is ready for use.

DIAMOND

MANUFACTURED BY:
Diamond Animal Health, Inc.
Des Moines, IA 50237
U.S. Veterinary License No. 213
Made in U.S.A.

DISTRIBUTED BY:
Bayer HealthCare LLC,
Animal Health Division
P.O. Box 390
Shawnee Mission, KS
66201 U.S.A.
1-800-633-3796

Bayer

83944706, R.0 83944722, R.0 83944730, R.0

This product is based on technology developed by Juvaris BioTherapeutics and is patent protected. Animal health applications are being exclusively developed by Bayer HealthCare Animal Health and are protected by Bayer patent applications.

 52405B

Elanco™

[1] Blondeau JM. 2011. "STAT – Steps to Antimicrobial Therapy; The Mutant Prevention Concentration – A Strategy to Optimize Therapy for Bacterial Infections in Cattle & Swine." Port Huron, MI: North American Compendiums Inc.; 184.

[2] Griffin, D., Chengappa, M. et al. July 2010. "Bacterial pathogens of the bovine respiratory disease complex." Veterinary Clinics of North America: Food Animal Practice. 26.2: 381-394.

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

IMPORTANT MICOTIL SAFETY INFORMATION

Before using this product, it is important to read the entire product insert, including the boxed human warning. Caution: Federal (USA) 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 female dairy cattle 20 months of age or older. 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 42 days.

Zelnate is based on technology developed by Juvaris BioTherapeutics and is patent protected. Animal health applications are being developed exclusively under the rights of Elanco and are protected by patents.