



## Efficacy of DRAXXIN<sup>®</sup> (tulathromycin) Injectable Solution for treatment of experimentally induced *Mycoplasma bovis* respiratory infection in calves

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### Key Points

- DRAXXIN<sup>®</sup> (tulathromycin) Injectable Solution administered as a single subcutaneous (SC) injection was safe and effective for the treatment of experimentally induced *Mycoplasma bovis* (*M. bovis*) respiratory infection in calves.
- DRAXXIN significantly reduced percentage of days with pyrexia and lung lesions compared with saline.
- Animals treated with DRAXXIN gained more weight than animals treated with saline in one study.
- *M. bovis* can be a major contributor to acute and chronic pneumonia in feeder cattle.

### Introduction

DRAXXIN contains the active ingredient tulathromycin, the first of a new subclass of macrolide, the triamilides, discovered and developed by Pfizer Animal Health for use in livestock. DRAXXIN is a highly effective, single-dose antimicrobial medication indicated for treatment of bovine respiratory disease (BRD) caused by *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*, and control of respiratory disease in cattle at high risk of developing BRD caused by *M. haemolytica*, *P. multocida*, and *H. somni*.

DRAXXIN is formulated to have excellent syringeability, even at low temperatures, and a convenient low-volume dose (1 mL/40 kg; 1.1 mL/100 lb). When administered according to the label dose of 2.5 mg tulathromycin/kg body weight (BW), tulathromycin is rapidly absorbed, distributes widely, and provides concentrations in bovine lung for an extended period.<sup>1</sup> Clinical efficacy of DRAXXIN for treatment of BRD, as well as for control of respiratory disease in cattle at high risk of developing BRD, has been well documented in multiple studies.<sup>2,3,4</sup> In pivotal



studies,<sup>5</sup> *Mycoplasma* species were isolated almost as frequently as *M. haemolytica* from animals with clinical BRD.

In general, *Mycoplasma* species cause slowly progressive, indolent respiratory tract lesions in the species they infect. Typically they initially colonize respiratory mucosal surfaces, interfering with ciliary function and eliciting chronic airway inflammation leading to chronic airway disease, which enhances bacterial colonization.<sup>6</sup> *Mycoplasma* respiratory disease in most species, particularly swine and laboratory mice, shows inconspicuous clinical signs initially, which usually leads to substantial lung involvement before clinical signs of disease are readily apparent. Infected animals are typically colonized for long periods of time, which facilitates spread within populations and increases infection rates before disease is recognized and therapeutic intervention occurs. Anecdotal evidence indicates that this may occur to some extent in cattle as well. Studies in other species demonstrate that *Mycoplasma* infection augments severity of subsequent respiratory infection with other bacteria and viruses.<sup>7,8,9</sup>

Multiple studies and years of field observations have confirmed *M. bovis* as one of the most common etiologic agents isolated from chronic non-responsive bronchopneumonia in feedlot cattle. Its role in acute respiratory disease has been less clear until recently.<sup>10,11,12</sup> Recent studies solidify the role of *M. bovis* as a contributor in both acute and chronic pneumonia in feedlot cattle. *M. bovis* was isolated from 85% of lungs of cattle with acute fibrinous pneumonia and 98% of chronic pneumonias in 1 study.<sup>13</sup> Previous studies had demonstrated that challenge with *M. bovis* 24 hours prior to challenge with *M. haemolytica* substantially increases lung lesion severity and mortality, above that seen with *M. haemolytica* challenge followed by *M. bovis* challenge.<sup>14</sup>

Mounting evidence indicates that *M. bovis* can be a major contributor to acute and chronic pneumonia in some classes of feeder cattle, requiring better management of *M. bovis* in treatment and control of BRD in feedlot cattle. To that end, additional research has since documented the efficacy of DRAXXIN in the treatment of experimentally induced BRD caused by *M. bovis*. DRAXXIN is the only antimicrobial approved in the U.S. for treatment of BRD caused by *M. bovis*.

This technical bulletin presents the results of two challenge studies in which calves were experimentally infected with *M. bovis* and then treated with DRAXXIN or saline. Study 1 was conducted in the United Kingdom utilizing Kansas State University *M. bovis* isolates. Study 2 was conducted in Nebraska utilizing a similar challenge model with a strain of *M. bovis* isolated from a naturally occurring case of BRD. The challenge isolate for study 2 was chosen from a candidate list of 6 clinical *M. bovis* isolates based upon their ability to induce a febrile response in cattle.

## Study 1

### Materials and Methods

Investigators obtained 109 crossbred Holstein calves, 3 to 9 weeks of age and weighing 94 to 169 lb (43 to 77 kg), from local farms. Serology and polymerase chain reaction (PCR) testing confirmed that all calves were free of *M. bovis* infection before inoculation. A 12-mL culture ( $1 \times 10^8$  CFU/mL) of *M. bovis* Strain 16150, isolated at Kansas State University, was administered via an endoscope to each calf on 3 consecutive days (Figure 1). Animals were eligible for enrollment within 5 days of the last inoculation when they showed clinical signs of BRD, including pyrexia ( $>39.5^\circ\text{C}/103.1^\circ\text{F}$ ) and abnormal respiration. Calves were allocated randomly to 1 of 2 treatments: saline at 0.025 mL/kg BW (35 animals) or DRAXXIN at 2.5 mg/kg BW (35 animals). Treatments were administered SC once on study Day 0. Animals were observed daily for clinical signs of respiratory disease, including pyrexia, abnormal respiration, and depression, by an experienced assessor who was unaware of the treatment allocation. At necropsy on day 14, the percentage of total lung with lesions typical of *M. bovis* infection was determined using the method of Jericho and Langford.<sup>15</sup> In addition, lung lavage samples were collected for recovery and quantification (CFU) of *M. bovis* and for confirmation of the presence of *M. bovis* by PCR testing.

Figure 1. Study 1 Experimental Design

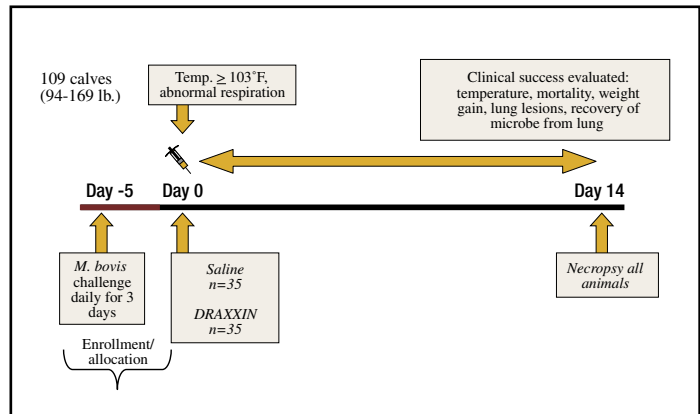
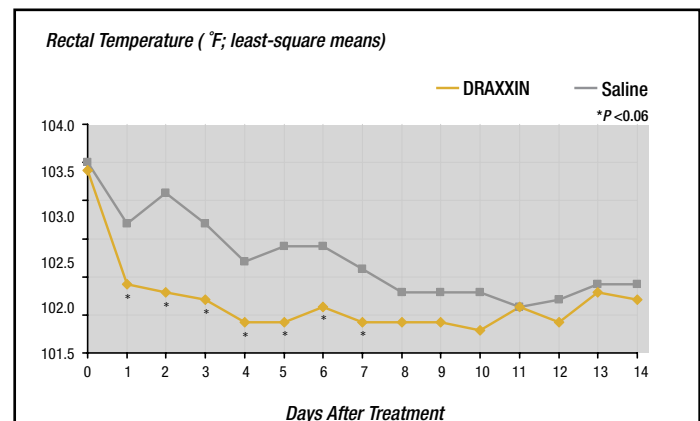


Figure 2. Mean Rectal Temperature for Calves in Study 1



Efficacy was assessed statistically on the basis of the percentage of total lung with lesions typical of a *M. bovis* infection, mortality, duration of post-treatment pyrexia, peak rectal temperature, body weight gains, and isolation of *M. bovis*. Prevalence and severity of clinical signs of respiratory disease and presence of other respiratory pathogens from bronchial lavage samples were summarized. The 5% level of significance was used to assess statistical differences for all tests.

## Results

*M. bovis* was recovered from the lung lavage samples of 66 animals, 34 in the saline group and 32 in the DRAXXIN group. The number of *M. bovis* recovered from lung lavage at necropsy was significantly ( $P=0.0084$ ) lower in the animals treated with DRAXXIN ( $10^{5.8}$  CFU/mL) than in those treated with saline ( $10^{6.5}$  CFU/mL). *P. multocida* was recovered in very low numbers from the lung lavage samples of 33 animals, 22 in the saline group (mean 696 CFU/mL) and 11 in the DRAXXIN group (mean 100 CFU/mL). No other bacteria were recovered during the study.

Nineteen animals (51.4%) in the saline group were euthanized due to severe clinical signs of respiratory disease. Mortality was significantly ( $P<0.0001$ ) lower in the DRAXXIN group (2.9%, 1/35) than in the saline group (51.4%, 18/35). Lung lesions were consistent with *M. bovis* induced pneumonia. The mean lung lesion scores were significantly ( $P=0.0001$ ) higher in the saline group (28.9%) than in the DRAXXIN group (11.3%).

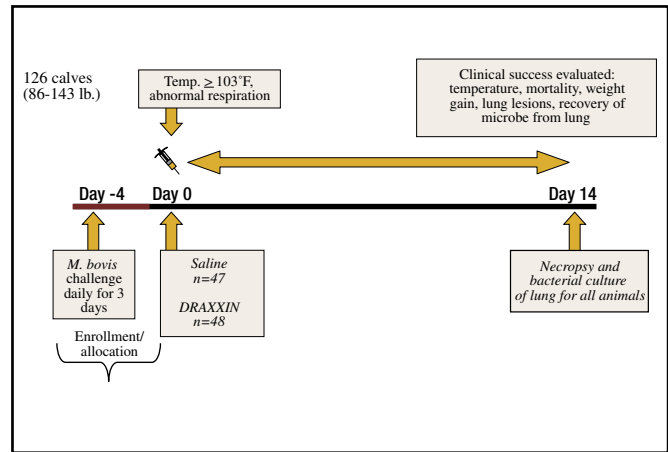
Animals treated with DRAXXIN showed a significant ( $P<0.05$ ) reduction in rectal temperature compared to animals treated with saline from study Day 1 to study Day 7 inclusive (Figure 2). The difference between the 2 treatments was significant for peak rectal temperature ( $P=0.0033$ ,  $40.2^{\circ}\text{C}/104.3^{\circ}\text{F}$  in the saline group vs.  $39.7^{\circ}\text{C}/103.5^{\circ}\text{F}$  in the DRAXXIN group) and for the duration of pyrexia ( $P=0.0074$ , 2.6 days vs. 1.2 days, respectively). There were no differences in the distribution of respiratory clinical signs of abnormal respiration between treatments ( $P=0.2665$ ) and there was no treatment by day interaction ( $P=0.6629$ ). There were no differences in the distribution of respiratory clinical signs of depression between treatments ( $P=0.5445$ ) and there was no treatment by day interaction ( $P=0.7935$ ). A priori contrasts to compare day of study for each treatment showed significant ( $P=0.0003$ ) reduction of clinical signs of depression from Day 0 to Day 14 in animals treated with DRAXXIN. The weight gains were lower in animals treated with saline (6.7 kg) than in animals treated with DRAXXIN (8.8 kg); this difference was not significant ( $P=0.0786$ ). DRAXXIN administered as a single dose of 2.5 mg/kg BW was highly effective in the treatment of induced *M. bovis* respiratory disease as gauged by marked reduction in mortality, lung lesion volume, *Mycoplasma* recovery, and mean peak temperature.

## Study 2

### Materials and Methods

The challenge model used in this study was originally developed by using 48 Holstein calves, 6 to 9 weeks of age, and 6 *M. bovis* isolates or growth media. Only 2 isolates were capable of soliciting a febrile response ( $>103^{\circ}\text{F}$ ). The percentage of pneumonic lung lesions in animals infected with *M. bovis* (4.5% to 35.2%) vs. media (0.3%) demonstrated that the lesions were indeed produced by the *M. bovis*.

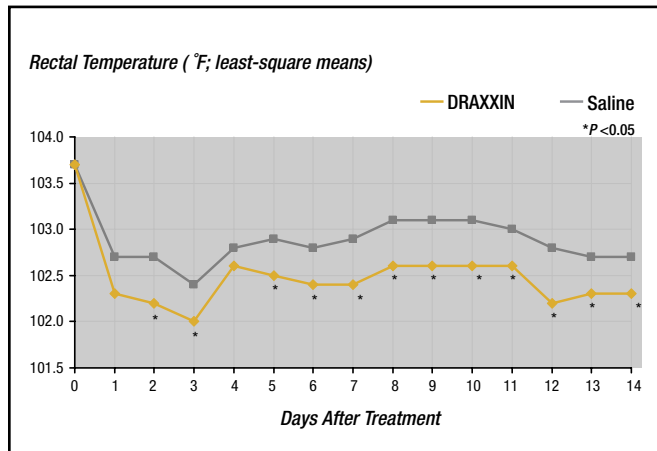
**Figure 3. Study 2 Experimental Design**



A study pool of 126 Holstein bull calves, 4 to 9 weeks of age and weighing 86 to 143 lb (39 to 65 kg), was confirmed free of *M. bovis* by both serology and nasopharyngeal swab PCR. Eligible calves were inoculated with *M. bovis* endotracheally, using an endoscope inserted nasally, for 3 consecutive days (Figure 3). The day following the last inoculation, each calf was assigned a respiratory score and had its rectal temperature measured. The first 96 calves with a rectal temperature  $\geq 103^{\circ}\text{F}$  and a respiratory score  $\geq 1$  (scale: 0=normal; 1=slightly increased respiration rate and/or slightly abnormal character; 2=moderately increased respiration rate and/or moderately abnormal character; 3=severely increased respiration rate and/or markedly abnormal character) were randomly assigned to receive a single injection of either saline at 0.025 mL/kg or tulathromycin at 2.5 mg/kg BW. Full enrollment occurred in 1 day. Day 0 was defined as the day of enrollment, allotment and administration of test article. Calves were individually penned. The investigator and clinical veterinarian remained masked to treatment and conducted all clinical assessments including postmortem observations. On Days 1 through 14, each calf was assigned a respiratory score and an attitude score (scale: 0=normal; 1=mild depression, reduced responsiveness and/or decreased appetite; 2=moderate to marked depression, may be reluctant to stand; 3=moribund, unable to stand without assistance). Rectal temperatures were also recorded each day. Calves were observed daily and euthanized 14 days post-treatment. The primary end point was percentage of pneumonic lung lesions.

## Results

Cultures from lung tissues identified *M. haemolytica* in 2 calves from each treatment group, *P. multocida* in 9 animals treated with saline and 4 animals treated with DRAXXIN, and *H. somni* in 2 animals treated with saline. *M. bovis* was recovered from all animals treated with saline and 26 animals treated with DRAXXIN.



**Figure 4.** Mean Rectal Temperature for Calves in Study 2

There were no mortalities. Animals treated with DRAXXIN had significantly less ( $P < 0.0001$ ) total lung lesions at Day 14 than did animals treated with saline (15.0% vs. 30.7%). In addition, animals treated with DRAXXIN had a reduced percentage of days with pyrexia (19.0% vs. 37.3%,  $P = 0.003$ ), fewer days with abnormal attitude scores (39.3% vs. 72.3%,  $P < 0.0001$ ), and fewer days with abnormal respiratory scores (49.9% vs. 88.3%,  $P < 0.0001$ ) than did animals treated with saline. The mean rectal temperature of calves receiving DRAXXIN was the same (103.7°F vs. 103.7°F,  $P = 0.75$ ) as that of animals treated with saline on Day 0 but was significantly less ( $P < 0.05$ ) on 12 of the 14 post-treatment days (Figure 4); there were no significant differences ( $P \geq 0.06$ ) in rectal temperature between treatment groups on Days 1 and 4. Animals treated with DRAXXIN gained significantly more weight during the 14-day post-treatment period than did animals treated with saline (10.3 vs. 4.7 lb,  $P = 0.0002$ ).

DRAXXIN was effective and safe for the treatment of experimentally induced respiratory disease associated with *M. bovis*.

## Discussion

The association of *M. bovis* with respiratory disease in cattle has been obvious for decades; however, the evolving question is to what extent *M. bovis* contributes to the early events of BRD. Evidence from other studies cited earlier suggests that *M. bovis*

can predispose to more severe bacterial respiratory infection and may be a significant component of acute as well as chronic BRD in some classes of cattle. Furthermore, the magnitude and severity of pneumonia caused by *M. bovis* in these studies provides evidence that it merits respect as a respiratory pathogen of cattle. It seems prudent to consider that comprehensive treatment of acute BRD should consider effectiveness against *M. bovis* as a criterion for anti-infective selection in high-risk cattle, especially in circumstances where response to traditional antibiotic therapy is less than anticipated. Isolation of other bacteria from lungs at necropsy could be due to: a) contamination during nasal passage of the endoscope at challenge inoculation; or b) predisposition of lung infected with *M. bovis* to infection by other pathogens, as has been demonstrated with mycoplasmas in other species.

It is obvious that none of the microbiological contributors to BRD operate independently and that single-agent inoculation studies may not cause the full spectrum of events occurring in natural BRD. It should be recognized, however, that DRAXXIN is labeled for treatment and control of the four major BRD bacterial pathogens, and has exhibited superior clinical efficacy against naturally occurring BRD in multiple clinical studies.<sup>2,3,4</sup> In the 2 studies presented here, DRAXXIN significantly reduced severity of pneumonic lesions and days of fever resulting from *M. bovis* pulmonary challenge. In study 1, DRAXXIN significantly reduced mortality from *M. bovis* challenge, from over 51.4% to 2.9%, indicating that this was both a robust challenge and that DRAXXIN was exceptionally effective in reducing mortality. There is evidence of difference in virulence among *M. bovis* isolates, which could explain the difference in mortality between these 2 studies. An important point to note is even though the challenge resulted in over 50% mortality in the control (saline-treated) group, the mean rectal temperatures never exceeded 103.5°F post challenge. In many production settings, rectal temperature is used as an aid in diagnosing disease, prescribing treatment, and evaluating treatment response. The relatively mild elevations seen in this study may indicate that rectal temperature is an unreliable indicator of disease caused by *M. bovis*, and it may have limited diagnostic utility when *M. bovis* is a factor in the Bovine Respiratory Disease Complex (BRDC).

## Conclusions

Results of these challenge studies provide evidence that DRAXXIN was effective for the treatment of experimentally induced *M. bovis* respiratory infection. DRAXXIN significantly reduced percentage of days with pyrexia and lung lesions in both studies compared with saline, and significantly reduced mortality in study 1. Animals treated with DRAXXIN gained more weight than animals treated with saline in study 2.

Do not use DRAXXIN in female dairy cattle 20 months of age or older. Effects on reproductive performance, pregnancy and

lactation have not been determined. Do not use in calves to be processed for veal. Do not use in chickens or turkeys. Do not use in animals known to be hypersensitive to the product.

Prepared from study reports 513E-03-03-264, 1131C-60-04-441, and 1131C-60-04-442.

## References

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# Draxxin<sup>®</sup>

(tulathromycin)  
Injectable Solution

Antibiotic  
100 mg of tulathromycin/mL

For subcutaneous injection in beef and non-lactating dairy cattle and intramuscular injection in swine only.

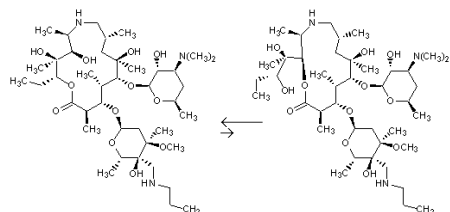
**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

### DESCRIPTION

DRAXXIN Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass, trimilide. Each mL of DRAXXIN contains 100 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monohydroxyglycerol (5 mg/mL), with citric and hydrochloric acids added to adjust pH.

DRAXXIN 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,6R,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 (2S,3S,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyranosyl]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-azacyclopentadecan-13-one, respectively.

### INDICATIONS

#### Cattle

DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*) and *Mycoplasma bovis*; and for the control of respiratory disease in cattle at high risk of developing BRD, associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* (*Haemophilus somnus*).

#### Swine

DRAXXIN Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica* and *Haemophilus parasuis*.

### DOSAGE AND ADMINISTRATION

#### Cattle

Inject subcutaneously as a single dose in the neck of cattle 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. DRAXXIN 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

#### Swine

Inject intramuscularly as a single dose in the neck of swine at a dosage of 2.5 mg/kg (0.25 mL/22 lb) BW. Do not inject more than 2.5 mL per injection site.

Table 2. DRAXXIN Swine Dosing Guide

Animal Weight (Pounds)	Dose Volume (mL)
15	0.2
30	0.3
50	0.6
70	0.8
90	1.0
110	1.3
130	1.5
150	1.7
170	1.9
190	2.2
210	2.4
230	2.6
250	2.8
270	3.1
290	3.3

### CONTRAINDICATIONS

The use of DRAXXIN 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. Do not use in female dairy cattle 20 months of age or older. 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

Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

### PRECAUTIONS

#### Cattle

The effects of DRAXXIN 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.

#### Swine

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

### ADVERSE REACTIONS

#### Cattle

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

#### Swine

In one field study, one out of 40 pigs treated with DRAXXIN at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

### 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.<sup>1</sup> 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.<sup>2</sup> 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 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.

#### 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.<sup>3</sup> 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.

#### Swine

Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed ( $T_{max} \sim 0.25$  hour). Subsequently, the drug rapidly distributes into body tissues, achieving a volume of distribution exceeding 15 L/kg. The free drug is rapidly cleared from the systemic circulation ( $CL_{systemic} = 187$  mL/hr/kg). However, it has a long terminal elimination half-life (60 to 90 hours) owing to its extensive volume of distribution. Although pulmonary tulathromycin concentrations are substantially higher than concentrations observed in the plasma, the clinical significance of these findings is undetermined. There are no gender differences in swine tulathromycin pharmacokinetics.

### MICROBIOLOGY

#### Cattle

*In vitro* activity of tulathromycin has been demonstrated against *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* (*Haemophilus somnus*) and *Mycoplasma bovis*; four pathogens associated with BRD.

All minimum inhibitory concentration (MIC) values were determined using the 9:1 isomer ratio of this compound. The MICs of tulathromycin were determined for isolates obtained from animals enrolled in field studies in the U.S. during 1999.

Table 3. Tulathromycin MIC values from field studies evaluating BRD in the U.S.

Organism	No. Isolates	MIC <sub>90</sub> * (µg/mL)	MIC range (µg/mL)
<i>Mannheimia haemolytica</i> *	642	2.0	0.5 to 64.0
<i>Pasteurella multocida</i> *	221	1.0	0.25 to 64.0
<i>Histophilus somni</i> ( <i>Haemophilus somnus</i> )*	36	4.0	1.0 to 4.0

\*Clinical isolates supported by clinical data and indications for use.

#### Swine

*In vitro* activity of tulathromycin has been demonstrated against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, and *Haemophilus parasuis*, commonly isolated pathogens associated with SRD.

All minimum inhibitory concentration (MIC) values were determined using the 9:1 isomer ratio of this compound. The MICs of tulathromycin were deter-

Table 4. Tulathromycin MIC values from field studies evaluating SRD in the U.S. and Canada.

Organism	No. Isolates	MIC <sub>90</sub> * (µg/mL)	MIC range (µg/mL)
<i>Actinobacillus pleuropneumoniae</i>	135	32.0	16.0 to 32.0
<i>Haemophilus parasuis</i>	31	2.0	0.25 to >64.0
<i>Pasteurella multocida</i>	55	2.0	0.5 to >64.0
<i>Bordetella bronchiseptica</i>	42	8.0	2.0 to 8.0

\*The minimum inhibitory concentration for 90% of the isolates.

### EFFECTIVENESS

#### Cattle

In a multi-location field study, 314 calves with naturally occurring BRD were treated with DRAXXIN. 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  $\leq 104^{\circ}\text{F}$  on Day 14. The cure rate was significantly higher ( $P \leq 0.05$ ) in DRAXXIN-treated calves (78%) compared to saline-treated calves (24%). There were two BRD-related deaths in the DRAXXIN-treated calves compared to nine BRD-related deaths in the saline-treated calves.

In another multi-location field study with 399 calves at high risk of developing BRD, administration of DRAXXIN 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  $\leq 104^{\circ}\text{F}$  on Day 14. There were no BRD-related deaths in the DRAXXIN-treated calves compared to two BRD-related deaths in the saline-treated calves.

Fifty-two DRAXXIN-treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *M. bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 DRAXXIN-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.

Two induced infection model studies were conducted to confirm the effectiveness of DRAXXIN against *M. bovis*. A total of 166 calves were inoculated intratracheally with field strains of *M. bovis*. When calves became pyrexia and had abnormal respiration scores, they were treated with either DRAXXIN (2.5 mg/kg BW SC) or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the DRAXXIN-treated calves compared with saline-treated calves (11.3% vs. 28.9%,  $P = 0.0001$  and 15.0% vs. 30.7%,  $P < 0.0001$ ).

#### Swine

In a multi-location field study, 266 pigs with naturally occurring SRD were treated with DRAXXIN. Responses to treatment were compared to saline-treated controls. Success was defined as a pig with a normal attitude, normal respiration, and a rectal temperature of  $< 104^{\circ}\text{F}$  on Day 7. The treatment success rate was significantly greater ( $P \leq 0.05$ ) in DRAXXIN-treated pigs (70.5%) compared to saline-treated pigs (46.1%).

### ANIMAL SAFETY

#### Cattle

Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly treatments 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 once and two of six calves administered 15 mg/kg BW once.

A safety study was conducted in 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.

#### Swine

Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular doses of 2.5, 7.5 or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.

### STORAGE CONDITIONS

Store at or below 25°C (77°F).

### HOW SUPPLIED

DRAXXIN Injectable Solution is available in the following package sizes:  
100 mL vial  
250 mL vial  
500 mL vial

<sup>1</sup> Carbon C. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. *Clin Infect Dis* 1998;27:28-32.  
<sup>2</sup> Nightingale CJ. Pharmacokinetics and pharmacodynamics of newer macrolides. *Pediatr Infect Dis J* 1997;16:438-443.  
<sup>3</sup> Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/kg BW administered by either subcutaneous or intravenous injection.

U.S. Patents: See US 6,329,345; US 6,420,536; US 6,514,945; US 6,583,274; US 6,777,393

NADA 141-244, Approved by FDA

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To report a suspected adverse reaction call 1-800-366-5288.  
To request a material safety data sheet call 1-800-733-5500.  
For additional DRAXXIN product information call:



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