



Comparative efficacy of DRAXXIN™ or Micotil® for the control of respiratory disease in cattle at high risk of developing undifferentiated bovine respiratory disease

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Key Points

- DRAXXIN™ (tulathromycin) Injectable Solution administered as a single subcutaneous (SC) injection was safe and effective for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease (BRD) caused by *Mannheimia haemolytica*, *Histophilus somni* (*Haemophilus somnus*) and *Pasteurella multocida*.
- When DRAXXIN was administered during arrival processing in a multi-location (4 sites) short-term study and a 229-day feedlot study, fewer animals developed BRD, as demonstrated by defined clinical signs, than did cattle that received Micotil® (tilmicosin) Injection during arrival processing.
- Fewer animals that received DRAXXIN required multiple hospital treatments than did animals that received Micotil.
- In the 229-day feedlot study, fewer animals ($P=0.014$) that received DRAXXIN than received Micotil became BRD-associated removals (mortalities plus chronics) from days 3 through 28.

Introduction

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

DRAXXIN is formulated with excellent syringeability, even at low temperatures, and has a convenient low-volume dose (1mL/

40 kg; 1.1 mL/100 lb). When administered at the label dose of 2.5 mg tulathromycin/kg body weight (BW), tulathromycin is rapidly absorbed, distributes widely (large apparent volume of distribution) and provides concentrations in bovine lung for an extended period.¹ Clinical efficacy of DRAXXIN for control of respiratory disease in cattle at high risk of developing BRD has been well documented by results of multiple studies in feedlot and stocker settings.^{2,3,4}

Reported here are results of a multi-location (4 sites), short-term study submitted for regulatory approval of DRAXXIN and a



longer-term feedlot study that compared the efficacy of DRAXXIN with that of Micotil for the control of respiratory disease in cattle at high risk of developing BRD, and the subsequent feedlot performance and carcass characteristics of animals that completed the study.

Multi-location Short-term Study

Materials and Methods

During the fall and winter of 1999, feeder steers were acquired from multiple auction markets in Mississippi, Washington, Idaho, South Carolina, Kentucky, Missouri and California, were transported to 4 research feedlots (1 each in Texas, Nebraska, California and Idaho) and were at high risk of developing BRD. A common protocol was used so that the data could be pooled for analysis. Cattle were processed, typical for commercial feedlot practices, and enrolled in the study within 1 to 2 days of their arrival. Animals were randomly assigned to receive saline, DRAXXIN (2.5 mg tulathromycin/kg BW), or Micotil (10 mg tilmicosin/kg BW) once by SC injection at the time of processing. Calves from all study groups were commingled during the study.

On days 1 through 14, animals that were assigned abnormal respiratory and clinical attitude scores (CAS) were removed from study pens so that rectal temperatures could be measured and recorded. Calves with rectal temperatures <104°F were returned to their pens. Calves received their 1st hospital treatment if they exhibited, on days 1 through 14, abnormal CAS, abnormal respiratory score, and rectal temperatures ≥104°F. Clinical attitude scores were assigned as follows: 0 = normal, bright, alert, responsive; 1 = mild depression; 2 = moderate to marked depression (may be reluctant to stand); 3 = severe depression (unable to stand without assistance); 4 = moribund, unable to rise. Respiratory scores were assigned as follows: 0 = normal, 1 = abnormal. The primary clinical end point for this study was the determination of animals that required treatment, as per treatment criteria above, or that were BRD-associated mortalities. For purposes of this study an animal was

determined to be a clinical success if it did not meet those treatment criteria or was not classified as a BRD-related mortality. Animals that met treatment criteria received standard feedlot treatment and were returned to their pens.

Nasopharyngeal samples were obtained from animals in the saline-control group before they received their 1st hospital treatment, and were submitted to veterinary microbiological laboratories for isolation and identification of organisms associated with the outbreak of BRD.

This study was conducted and analyzed according to the experimental design contained in the study protocol, which included random allocation of animals to groups, response data to be analyzed, and statistical methods to be used.

Results

Twelve animals were removed for non-BRD reasons (4 that received saline, 3 that received DRAXXIN, and 5 that received Micotil). Clinical signs exhibited by animals that required treatment were typical of those for naturally occurring BRD. Morbidity was significantly

($P=0.0001$) lower for calves that received DRAXXIN (13.2%) than for those that received saline (58%) or Micotil (28.7%; Table 1). Microbiological results of samples from lungs of calves that died, or from nasopharyngeal swabs obtained from calves that received saline and required treatment, supported bacterial and mycoplasmal etiologies of the respiratory disease (Table 2).

No adverse drug-related experiences were reported.

229-Day Feedlot Study

Materials and Methods

During the fall of 2001, in a feedlot study, the efficacy of DRAXXIN or Micotil for the control of respiratory disease in cattle at high risk of developing BRD, and the subsequent performance and carcass characteristics of those cattle were compared (Figure 1). Five-hundred crossbred steers (430 to 714 lb, 195 to 325 kg) were acquired from auction markets in Colorado and Wyoming, were transported to a feedlot in Colorado and were at high risk for developing undifferentiated BRD. At arrival, 250 animals per group were

Table 1. Successes Following Administration of DRAXXIN, Micotil or Saline at Arrival Processing: Short-term Study, n (%)

	DRAXXIN	P Value	Micotil	P Value	Saline
Animals Enrolled*	n=410		n=408		n=409
No Observed BRD Through Day 14	356 (86.8%)	NA	291 (71.3%)	NA	171 (41.8%)
Animals Treated	54 (13.2%)	0.0001	117 (28.7%)	0.0001	236 (58.0%)
Mortalities	0 (0.0%)	NA	0 (0.0%)	NA	2 (0.5%)

*Number of animals enrolled minus non-BRD removals. NA = not analyzed.

Table 2. Pathogens Isolated at the Time of First Treatment from 226 of 236 Animals that Received Saline at Arrival Processing Plus 2 BRD Mortalities: Short-term Study, n (%)

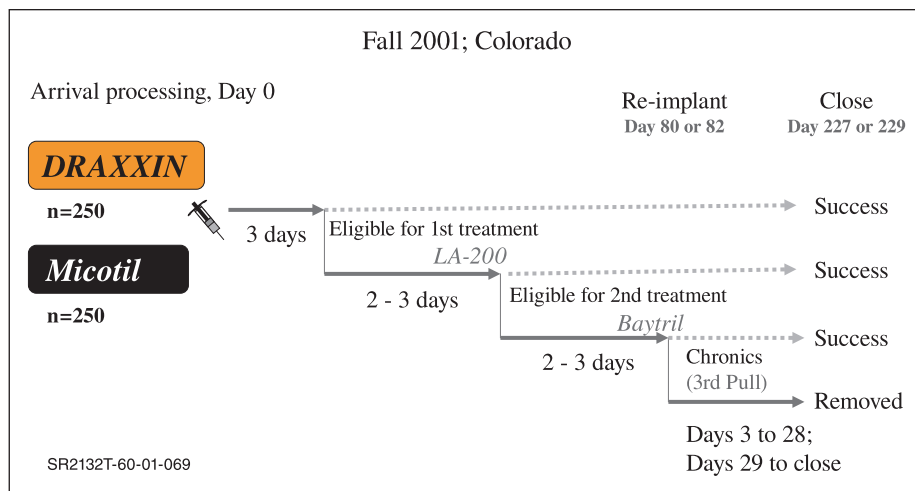
<i>M haemolytica</i>	<i>P multocida</i>	<i>H somnus</i>	<i>Mycoplasma</i> species
143 (63.3%)	60 (26.5%)	18 (8.0%)	123 (54.4%)

randomly assigned to receive DRAXXIN (2.5 mg tulathromycin/kg BW) or Micotil (10 mg tilmicosin/kg BW). There were 5 replicates per group, 50 animals per pen, 1 group per pen. Arrival processing also included administration of BOVI-SHIELD™ 4, DECTOMAX®, DURASECT® II, and Synovex® S Implants.

This study was divided into 2 phases, days 0 to 28 and day 29 to close. For days 3 through 28, hospital-treatment criteria included a CAS of 1 or 2 (see description above) and rectal temperature $\geq 104^\circ\text{F}$, or a CAS ≥ 3 . Throughout the study, animals requiring 1st hospital treatment received LA-200® (20 mg oxytetracycline/kg BW) and animals requiring 2nd hospital treatment received Baytril® (11 mg enrofloxacin/kg BW). Animals were allowed approximately 2 to 3 days following each treatment before subsequent treatment was administered. Animals that met the hospital-treatment criteria 3 times were classified as chronics and removed from the study. For days 29 to close, animals were treated if they demonstrated clinical signs of BRD, regardless of rectal temperature. The original treatment regimen for hospital treatment was used for those animals remaining in the study from day 29 to close.

Body weights for individual animals were recorded on day 0, if the animal required additional treatment, when an animal was removed from the study, and at re-implant. Re-implant occurred on day 80 or 82. All animals that completed the study were weighed individually and harvested on a single day, either day 227 or day 229, depending on day of enrollment. Hot carcass weight was recorded. After an overnight chill, yield and quality grades, kidney/pelvic/heart fat, marbling and ribeye area were recorded.

Figure 1. Experimental Design for the 229-Day Feedlot Study: DRAXXIN or Micotil



This study was conducted and analyzed according to the experimental design contained in the study protocol, which included random allocation of animals to groups, response data to be analyzed, and statistical methods to be used.

Results

Success for days 3 through 28 and days 3 through close was significantly higher ($P=0.001$) for animals that received DRAXXIN (94.8% and 80.3%, respectively) than for animals that received Micotil (80.3% and 62.8%, respectively; Table 3). Frequency distribution of 1st hospital treatments during days 3 to 28 (Figure 2a) revealed daily numerical differences for animals in each group. Cumulative distribution of 1st hospital treatments during days 3 to 28 (Figure 2b) revealed marked differences between groups when the day-to-day variability of the frequency distribution accumulated. Fewer animals that received DRAXXIN at arrival required hospital treatment than did those animals that received Micotil.

Because eligibility for hospital treatment was re-initiated on day 29, some animals received 4 hospital treatments before being classified as chronics and removed from the study. Removals (mortalities plus chronics) from days 3 through 28 ($P=0.014$) and days 3 through 222 ($P=0.094$) were lower for animals that received DRAXXIN (0% and 2.1%, respectively) than those for animals that received Micotil (2.4% and 5%, respectively; Table 3).

The average daily gain (ADG) at close was not significantly higher ($P=0.4528$) for animals that received DRAXXIN (3.57 lb) than for animals that received Micotil (3.55 lb; Table 4). Animals that received DRAXXIN yielded a least-squares mean carcass weight of 841.0 lb compared to a carcass weight of 845.5 lb for animals that received Micotil ($P=0.5322$; Table 5). Differences in individual carcass variables (yield grade, quality grade, kidney/pelvic/heart fat, marbling, ribeye area) were not statistically significant ($P>0.05$).

No adverse drug-related experiences were

Table 3. Successes for Arrival Processing and Hospital Treatment; 229-Day Feedlot Study: DRAXXIN or Micotil,* n (%)

Animals Enrolled	Days 3-28			Days 3-Close**		
	DRAXXIN (n=250)	P Value	Micotil (n=250)	DRAXXIN (n=250)	P Value	Micotil (n=250)
Successes[§]	237 (94.8%)	0.001	200 (80.3%)	191 (80.3%)	0.001	152 (62.8%)
1st Hospital treatment	11	NA	30	33	NA	54
2nd Hospital treatment	2	NA	13	8	NA	19
3rd Hospital treatment	0	NA	0	1	NA	3
4th Hospital treatment	NA	NA	NA	0	NA	2
BRD Removals[§]	0 (0.0%)	0.014	6 (2.4%)	5 (2.1%)	0.094	12 (5.0%)
Chronics	0	NA	4	3	NA	9
BRD Mortalities	0	NA	2	2	NA	3
Non-BRD Removals^{§§}	0	NA	1	12	NA	8

NA = not analyzed.

* Arrival Processing = DRAXXIN or Micotil

1st hospital treatment = animal met treatment criteria 1 time (LA-200)

2nd hospital treatment = animal met treatment criteria 2 times (Baytril)

3rd hospital treatment = animal met treatment criteria 3 times (classified as chronic and removed from study)

4th hospital treatment = animal met treatment criteria 4 times (classified as chronic and removed from study)

Chronic = received ≥ 3 hospital treatments and removed from study

Treatment Criteria

Days 3-28 - CAS of 1 or 2 and a rectal temperature of ≥104°F, or CAS of 3 or 4

Days >28 - CAS of ≥1

** Close was either day 227 or day 229.

§ All percents calculated with number enrolled minus non-BRD removals as denominator.

§§ Non-BRD removals included non-BRD-associated mortalities.

Figure 2a. Frequency Distribution of Animals that Received 1st Hospital Treatment by Day, from Days 3 through 28; 229-Day Feedlot Study (Colorado): DRAXXIN or Micotil

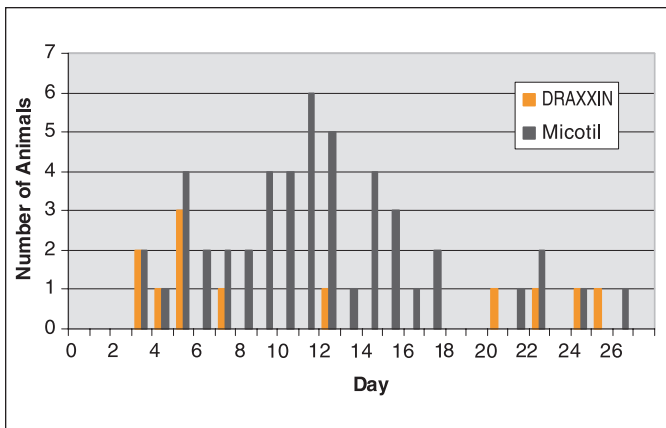


Figure 2b. Cumulative Distribution of Animals that Received 1st Hospital Treatment by Day, from Days 3 through 28; 229-Day Feedlot Study (Colorado): DRAXXIN or Micotil

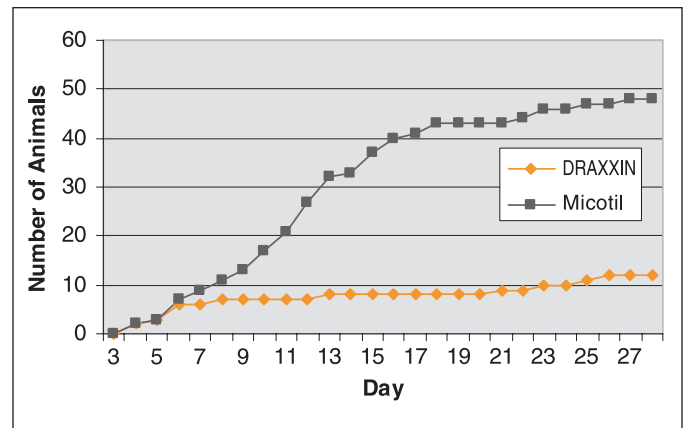


Table 4. Body Weights (lb),* Average Daily Gain (lb/day),* and Feed Efficiencies; 229-Day Feedlot Study: DRAXXIN or Micotil

	Days 0 to 80/82			Days 0 to 227/229		
	DRAXXIN	P Value	Micotil	DRAXXIN	P Value	Micotil
Initial Body Weight	543.0	0.3257	551.8	543.0	0.3257	551.8
Final Body Weight**	842.1	0.2515	834.4	1358.0	0.8559	1360.5
Average Daily Gain**	3.69	0.0914	3.49	3.57	0.4528	3.55
Feed Consumption[§]	14.96	0.2940	14.71	18.0	0.4310	18.15
Feed Conversion^{§§}	4.04	0.0536	4.22	5.03	0.0965	5.11

* Repeated measures mixed model least-squares mean estimates, based on pen-average body weight. Removals (mortalities plus chronics) are not included.

** Mortalities and chronics removed. Day 227/229 final body weight is an average based on pen weight.

§ Feed consumption: Pounds of feed calculated on a dry matter basis.

§§ Feed conversion: Pound of feed/pound of weight gain. Number of animal-days accounted for removals per time period.

Table 5. Carcass Adjusted Least-Squares Mean Final Body Weight, Weight Gain, Average Daily Gain, and Hot Carcass Weight at Close; 229-Day Feedlot Study: DRAXXIN or Micotil,* n (SEM)

	DRAXXIN	P Value	Micotil
Number of Animals	233		230
Final Body Weight, lb	1293.88 (7.42)	0.5322	1300.76 (7.47)
Weight Gain, lb	751.9 (6.24)	0.7311	749.1 (6.28)
Average Daily Gain, lb/day	3.37 (0.03)	0.7311	3.36 (0.03)
Hot Carcass Weight, lb	841.0 (4.82)	0.5322	845.5 (4.86)

* Mortalities and chronics removed.

Discussion

Animals used in these studies were at high risk of developing BRD and were randomly assigned to receive the respective medication so that the expected incidence of disease would be the same for both groups of animals. Bacteria isolated during the short-term study (*M haemolytica*, *P multocida* and *H somni*) were consistent with those associated with BRD.^{5,6} In addition, *Mycoplasma* species were isolated in 54% of sampled individuals (Table 1).

Based on number of animals that received hospital treatment and number of BRD removals (mortalities plus chronics), the results of the short-term, multi-location study are evidence of the efficacy of DRAXXIN for control of respiratory disease in cattle at high risk of developing BRD. Further evidence was provided by results of a 229-day feedlot study, based on number of animals that received hospital treatment (42 animals in the group that received DRAXXIN, 75 in the group that received Micotil) and number of BRD removals (mortalities plus chronics; 5 [2.1%] animals in the group that received DRAXXIN, 12 [5%] in the group that received Micotil).

The substantial response to 1st treatment with DRAXXIN was followed by fewer additional treatments than for cattle that received Micotil. That finding, in light of the different medications used for 1st and 2nd hospital treatment, suggests that the choice of medication for 1st treatment had a major influence on response to subsequent treatment. Frequency distribution and cumulative distribution for 1st treatments should be considered when evaluating clinical response to medication used for the control of BRD, because they provide excellent, though different, views of the same information.

Treatment criteria were consistent within each phase of the 229-day feedlot study, but were different in the first phase (days 3 through 28) from those in the second phase (days 29 through close). As a result, a few animals received 4 hospital treatments before being classified as chronics and removed from the study. Removals (mortalities plus chronics) from days 3 through 28 ($P=0.014$) and days 3 through 222 ($P=0.094$) were lower for animals that received DRAXXIN (0% and 2.1%, respectively) than those for animals that received Micotil (2.4% and 5%, respectively; Table 3). A P value of 0.094

indicates that there was a 90.6% probability that the difference in BRD removals was actually attributable to DRAXXIN.⁷ There was no difference in ADG for animals that completed the study in either of the 2 groups.

In order to minimize confounding influences on results, animals were randomly assigned to receive one of the respective medications being evaluated. Management practices and processing at each site of investigation were consistent for all animals within a given study. Recording of the disposition of animals removed from the studies (BRD-associated or non-BRD-associated removals) was not included in the protocol; therefore, that information is not available for analysis or discussion. Before each study began, regimens for administration of those medications as well as subsequent medication (if needed) were stated in the respective protocols. Criteria for administration of subsequent medication and for classifying the responses were also defined to be consistent within the study. Because those steps were implemented, results within a given study could be attributed to the respective medication being evaluated.

Conclusions

DRAXXIN administered as a single SC injection was safe and significantly more effective than was Micotil for the control of respiratory disease in cattle at high risk of developing BRD caused by *M haemolytica*, *H somni* and *P multocida*.

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.

References

- 1 Nowakowski MA, Inskeep P, Risk J, et al. Pharmacokinetics and lung tissue concentrations of tulathromycin, a new triamidine antibiotic, in cattle. *Vet Ther* 2004;5:60-74.
- 2 Rooney KA, Nutsch RG, Skogerboe TL, Weigel DJ, Kimberly K, Kilgore WR. Comparative efficacy of tulathromycin for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease. *Vet Ther* 2005; in press.
- 3 Nutsch RG, Skogerboe TL, Rooney KA, Weigel DJ, Gajewski K, Lechtenberg KF. Comparative efficacy of tulathromycin, tilimicosin and florfenicol in the treatment of bovine respiratory disease in stocker cattle. *Vet Ther* 2005; in press.
- 4 Skogerboe TL, Rooney KA, Nutsch RG, Weigel DJ, Gajewski K, Kilgore WR. Comparative efficacy of tulathromycin versus florfenicol and tilimicosin against undifferentiated bovine respiratory disease in feedlot cattle. *Vet Ther* 2005; in press.
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Prepared from studies 1133C-60-99-309, 1133C-60-99-310, 1133C-60-99-311, 1133C-60-99-312, and 2132T-60-01-069.



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Draxxin™

(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.

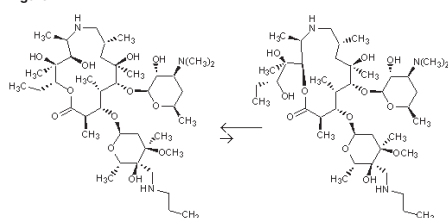
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

DRAXXIN Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass: triamline. Each mL of DRAXXIN contains 100 mg of tulathromycin as the free base in a 50% propylene glycol vehicle, monothioglycerol (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,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-xyllo-hexopyranosyl]-oxy]-1-oxa-6-azacyclotridecan-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-ribohexopyranosyl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-9-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xyllohexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Cattle
DRAXXIN Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*), 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*.

DOSE 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.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 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. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. *Clin Infect Dis* 1998; 27:28-32.
² Nightingale CJ. Pharmacokinetics and pharmacodynamics of newer macrolides. *Pediatr Infect Dis J* 1997; 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.

Swine

Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed ($T_{max} = 0.25$ 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* and *Histophilus somni* (*Haemophilus somnus*), the three major 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 ₉₀ [†] (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
<i>Mycoplasma bovis</i> **	35	1.0	≤0.063 to 2.0

[†]The minimum inhibitory concentration for 90% of the isolates.

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

**The correlation between *in vitro* susceptibility data and clinical response has not been confirmed.

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 determined for isolates obtained from swine enrolled in SRD field studies in the U.S. and Canada during 2000 through 2002.

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

Organism	No. Isolates	MIC ₉₀ [†] (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 ≤104°F on Day 14. The cure rate was significantly higher ($P < 0.05$) 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 ≤104°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.

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°F on Day 7. The treatment success rate was significantly greater ($P < 0.05$) 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

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

Distributed by:
 **Pfizer Animal Health**
Division of Pfizer Inc, NY, NY 10017

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:
1-888-DRAXXIN or go to **www.DRAXXIN.com**

TAKE
TIME
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DIRECTIONS

79-9947-00-0
March 2005