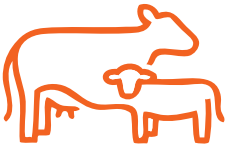
TECHNICAL BULLETIN



Comparative efficacy of DRAXXIN® or Nuflor® for the treatment of undifferentiated bovine respiratory disease in feeder cattle

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KEY POINTS

- DRAXXIN® (tulathromycin) Injectable Solution administered as a single subcutaneous (SC) injection was safe and effective for the treatment of undifferentiated bovine respiratory disease (BRD). DRAXXIN was significantly more effective, in 2 studies with feeder cattle, than was Nuflor® (florfenicol) Injectable Solution.
- First-treatment success, in both studies, for days 3 to 28 was significantly higher (P≤0.001, P=0.002) for cattle treated with DRAXXIN than for those treated with Nuflor. In Study 1, first-treatment success for animals that received DRAXXIN was 73.7% compared with 30.3% for those that received Nuflor. In Study 2, first-treatment success for animals that received DRAXXIN was 82% compared with 64% for those that received Nuflor.
- Removals associated with BRD (chronics plus mortalities), in both studies, were lower for the group that received DRAXXIN than for the group that received Nuflor. In one study, the difference was significant (P≤0.001).

INTRODUCTION

DRAXXIN contains the active ingredient tulathromycin, the first of a subclass of macrolide, the triamilides, discovered and developed by Zoetis for use in livestock. 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 *Mannheimia haemolytica, Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*.

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 (large apparent volume of distribution) and provides concentrations in bovine lung for an extended period.[1] 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 feedlot and stocker studies.[2,3,4]

Reported here are results of 2 studies that compared the efficacy of DRAXXIN with that of Nuflor for the treatment of undifferentiated BRD in cattle and their subsequent feedlot performance and carcass characteristics.

Study 1

Materials and Methods

In the spring of 2003, crossbred feeder steers (315 to 581 lb, 143 to 264 kg) purchased from auction markets in Minnesota, North Dakota, and Kansas, were transported to the study site in Nebraska, and processed (Figure 1). Processing at arrival included administration of BOVISHIELD™ 4, DECTOMAX® Injectable Solution, ULTRABAC® 7, and Ralgro® Implants. Animals were observed daily and those exhibiting clinical signs of BRD were examined further. Clinical attitude scores (CAS) 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. Calves that had a CAS ≥1 and rectal temperature ≥104°F were selected by the investigator and randomly assigned, during 2 consecutive days, to receive treatment with a single dose of DRAXXIN (2.5 mg tulathromycin/kg BW) SC (n=100) or Nuflor (40 mg florfenicol/kg BW) SC (n=100). Day 0 was the day of enrollment and first treatment for each calf. Nasopharyngeal samples for bacterial isolation and identification were obtained from 20% of animals, randomly selected from each group, prior to treatment.

Body weights for individual animals were recorded on day 0 (the day treatment was administered), if the animal required additional treatment, when an animal was removed from the study, day 28, at re-implanting on day 139 or 140, and at harvest on day 316 or 317.

From days 3 through 28, a CAS was recorded daily for each animal, and those fulfilling re-treatment criteria (CAS of 1 or 2 plus a rectal temperature ≥104°F, or a CAS of 3 or 4) received their 1st re treatment (LA-200®, 20 mg oxytetracycline/kg BW). Animals fulfilling these re-treatment criteria a second time received a 2nd retreatment (Baytril®, 11 mg enrofloxacin/kg BW). Re-treated animals were observed daily, but received no other treatment for 3 days following each re-treatment (with LA-200 or Baytril). From day 29 to close, animals that exhibited clinical signs of BRD (CAS of 1, 2, 3 or 4, regardless of rectal temperature) met re-treatment criteria. Animals that were re-treated 3 times during days 3 through 28 or 3 times between day 29 and close were classified as chronics and removed from the study. All remaining cattle were harvested on day 316 or 317, depending on the day of enrollment.

The 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 for Study 1

First-treatment success[5] for cattle treated with DRAXXIN was significantly higher ($P \leq 0.001$) than for cattle treated with Nuflor (days 3 through 28: DRAXXIN, 73.7%, Nuflor, 30.3%; days 29 through close: DRAXXIN, 53.2%, Nuflor, 23.2%; Table 1). Frequency distribution of 1st re-treatments during days 3 to 28 (Figure 2a) revealed daily numerical differences for animals in each treatment group. Cumulative distribution of 1st re-treatments during days 3 to 28 (Figure 2b) revealed marked differences among treatment groups when the day-to-day variability o the frequency distribution accumulated. Overall, fewer animals that received first treatment with DRAXXIN

required re-treatment than did those animals that received first treatment with Nuflor.

Removals due to BRD (chronics plus mortalities) were significantly lower (P≤0.001) for cattle treated with DRAXXIN than for cattle treated with Nuflor (days 3 through 28: DRAXXIN, 5.1%, Nuflor, 26.3%; days 3 through close: DRAXXIN, 20.2%, Nuflor, 47.5%; Table 1). During days 3 through close, 24 more cattle treated with Nuflor (42) were classified as chronics[6] and removed from the study than those treated with DRAXXIN (18; Table 1). More cattle that were treated with Nuflor (5) died due to BRD than those treated with DRAXXIN (1; Table 1).

Average daily gain, calculated with mortalities and chronics removed, from days 0 through 28 was significantly higher (P=0.0001) for cattle treated with DRAXXIN (3.46 lb/day) than for cattle treated with Nuflor (2.40 lb/day). There was no significant difference (P=0.3877) for ADG from day 0 through close for the surviving cattle that received DRAXXIN or Nuflor (Table 2). There were no significant differences (P>0.05) for final live body weights, hot carcass weights (Table 3) or individual carcass variables (kidney/pelvic/heart fat, fat thickness, marbling score, ribeye area, carcass quality and yield grades recorded after an overnight chill).

Nasopharyngeal samples from 21 animals and pulmonary samples from 2 animals yielded P multocida, M haemolytica and H somni species with 9, 13, and 2 isolates, respectively. Samples from some animals yielded more than 1 organism.

No adverse product-related experiences were reported.

Figure 1. Experimental Design of Treatment Study 1 (Nebraska); DRAXXIN or Nuflor

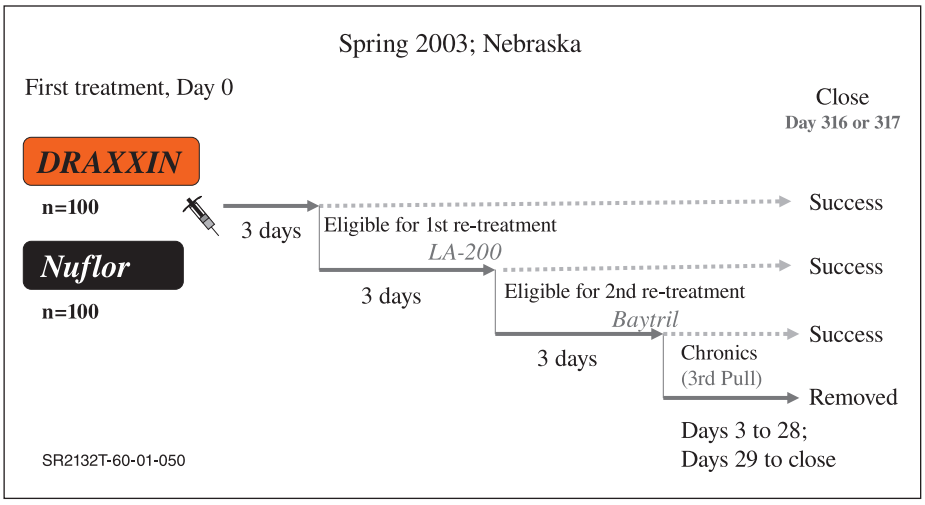


Table 1. First-treatment and Re-treatment Successes for Treatment Study 1; DRAXXIN or Nuflor,* n (%)

	Days 3-28			Days 3-Close**		
Success	**DRAXXIN** (n=100)	***P* Value**	**Nuflor** (n=100)	**DRAXXIN** (n=100)	***P* Value**	**Nuflor** (n=100)
First Treatment§	73 (73.7%)	0.001	30 (30.3%)	50 (53.2%)	0.001	23 (23.2%)
1st Re-treatment	13	NA	20	7	NA	11
2nd Re-treatment	8	NA	23	12	NA	11
3rd Re-treatment	0	NA	0	4	NA	4
4th Re-treatment	0	NA	0	2	NA	3
BRD Removals§	5 (5.1%)	0.001	26 (26.3%)	19 (20.2%)	0.001	47 (47.5%)
Chronics	5	NA	21	18	NA	42
BRD Mortalities	0	NA	5	1	NA	5
Non-BRD Removals§§	1	NA	1	6	NA	1

NA = not analyzed.

* First Treatment = DRAXXIN or Nuflor

1st re-treatment = LA-200 (20 mg oxytetracycline/kg BW)

2nd re-treatment = Baytril (11 mg enrofloxacin/kg BW)

3rd re-treatment = standard feedlot treatment and animal removed from study

4th re-treatment = standard feedlot treatment and animal removed from study

Chronic = received ≥3 re-treatments and removed from study

Re-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 316 or day 317 depending on day of enrollment.

§ BRD-associated mortalities and chronics. 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 Their 1st Re-treatment by Day, from Day 3 through Day 28; Treatment Study 1 (Nebraska); DRAXXIN or Nuflor

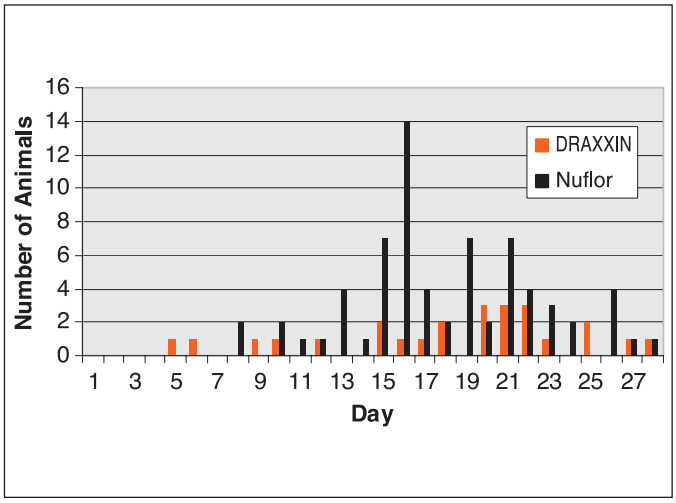


Figure 2b. Cumulative Distribution of Animals that Received Their 1st Re-treatment by Day, from Day 3 through Day 28; Treatment Study 1 (Nebraska); DRAXXIN or Nuflor

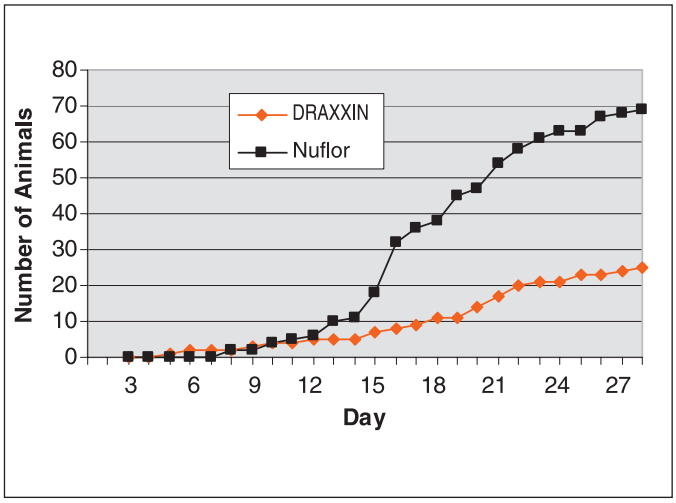


Table 2. Body Weight and Average Daily Gain for Animals that Remained in Treatment Study 1 (Nebraska); DRAXXIN or Nuflor

	Initial Body Weight* (lb)			Final Body Weight (lb)		Average Daily Gain* (lb/day)		
Days	**DRAXXIN**	***P* Value**	**Nuflor**	**DRAXXIN**	**Nuflor**	**DRAXXIN**	***P* Value**	**Nuflor**
0-28	437.1	0.5306	441.8	534.1	509.0	3.46	0.0001	2.40
28-Re-implant**	534.1	0.0074	509.0	878.2	850.4	3.07	0.7836	3.05
Re-implant-Close†	878.2	0.0556	850.4	1417.2	1404.0	3.05	0.3772	3.13
0-Close	437.1	0.5446	441.8	1417.2	1404.0	3.09	0.3877	3.04

* Least-Squares Mean. Repeated measures mixed model least-squares mean estimates of body weight and average daily gain did not include values for animals removed before day 28, or for mortalities or chronics removed prior to the day of re-implant or the day of harvest.
Note: Mortalities and chronics removed.
** Re-implant occurred on day 139 or day 140.
† Close was day 316 or day 317 depending on day of enrollment.

Table 3. Carcass Adjusted Least-Squares Mean Final Body Weight, Weight Gain, Average Daily Gain and Hot Carcass Weight to Close* for Animals that Remained in Treatment Study 1 (Nebraska); DRAXXIN or Nuflor, n (SEM)

	DRAXXIN	*P* Value	Nuflor
Number of Animals	75		52
Final Body Weight, lb	1378.0 (15.6)	0.8194	1372.4 (18.7)
Weight Gain, lb	937.8 (14.15)	0.7161	929.7 (16.99)
Average Daily Gain, lb/day	2.95 (0.04)	0.7161	2.93 (0.05)
Hot Carcass Weight, lb	895.7 (10.1)	0.8194	892.1 (12.2)

* Mortalities and chronics removed.

Study 2

Materials and Methods

Another study was performed in the spring of 2003 with feeder steers (348 to 692 lb, 158 to 314.5 kg) purchased from auction markets in Tennessee and transported to the study site in Colorado (Figure 3). Processing at arrival included administration of BOVI-SHIELD™ IBR/BVD, DECTOMAX, and Component® E-S Implant. Calves that had a CAS ≥1 and rectal temperature ≥104°F were selected by the investigator and randomly assigned, during 3 consecutive days, to receive treatment with a single dose of DRAXXIN (2.5 mg tulathromycin/kg BW) SC (n=100) or Nuflor (40 mg florfenicol/kg BW) SC (n=100). Animals from each treatment group (DRAXXIN or Nuflor) were commingled.

Cattle with a CAS of 1 or 2 plus a rectal temperature ≥104°F, or a CAS of 3 or 4, and that were at least 3 days post-treatment with DRAXXIN or Nuflor received their 1st re-treatment with ADVOCIN® (6 mg danofloxacin/kg BW), followed approximately 48 hours later by a second dose (6 mg danofloxacin/kg BW). Animals received no other treatment between the 2 doses of ADVOCIN. Animals fulfilling these re-treatment criteria a second time, and that were at least 2 days following the second dose of ADVOCIN, received their

Figure 3. Experimental Design of Treatment Study 2 (Colorado); DRAXXIN or Nuflor

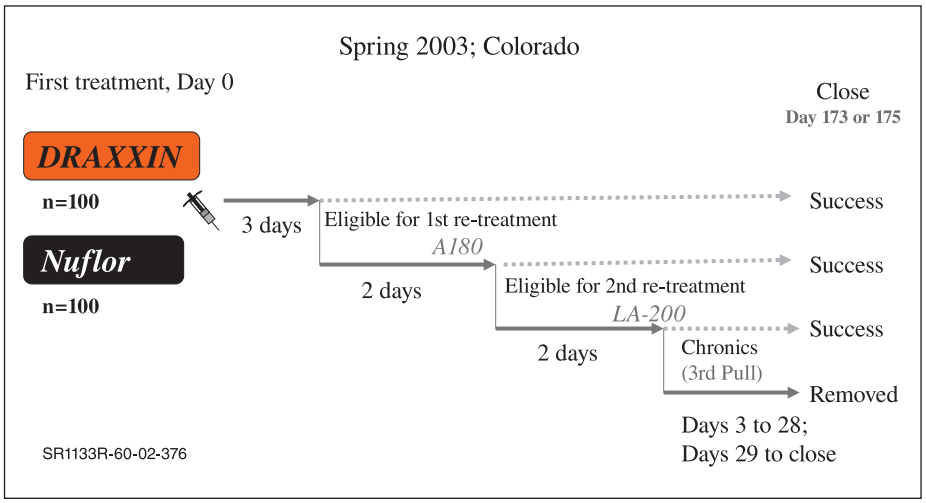


Table 4. Treatment and Re-treatment Successes*; Field Study 2 (Colorado): DRAXXIN or Nuflor, n (%)

	Days 3-28			Days 3-Close**		
Success	**DRAXXIN** (n=100)	***P* Value**	**Nuflor** (n=100)	**DRAXXIN** (n=100)	***P* Value**	**Nuflor** (n=100)
First Treatment§	82 (82%)	0.002	64 (64%)	77 (79.4%)	0.009	63 (63.6%)
1st Re-treatment	13	NA	23	12	NA	19
2nd Re-treatment	2	NA	4	3	NA	6
3rd Re-treatment	0	NA	0	1	NA	1
4th Re-treatment	0	NA	0	0	NA	0
BRD Removals§	3 (3%)	0.058	9 (9%)	4 (4.1%)	0.058	10 (10.1%)
Chronics	3	NA	9	3	NA	10
BRD Mortalities	0	NA	0	1	NA	0
Non-BRD Removals§§	0	NA	0	3	NA	1

NA = not analyzed.
* First Treatment = DRAXXIN or Nuflor
1st re-treatment = A180 (2 doses, 6 mg danofloxacin/kg BW with approximately 48-hour interval)
2nd re-treatment = LA-200 (20 mg oxytetracycline/kg BW)
3rd re-treatment = standard feedlot treatment and animal removed from study
4th re-treatment = standard feedlot treatment and animal removed from study
Chronic = received ≥3 re-treatments and removed from study
Re-treatment Criteria
Days 3-28 and days 29 to close - CAS of 1 or 2 and a rectal temperature of ≥104ºF; or CAS of 3 or 4
** Close was day 173 to 175 (mean = 173).
§ BRD-associated mortalities and chronics. All percents calculated with number enrolled minus non-BRD removals as denominator.
§§ Non-BRD removals included non-BRD associated-mortalities.

Figure 4a. Frequency Distribution of Animals that Received Their 1st Re-treatment by Day, from Day 3 through Day 28; Treatment Study 2 (Colorado): DRAXXIN or Nuflor

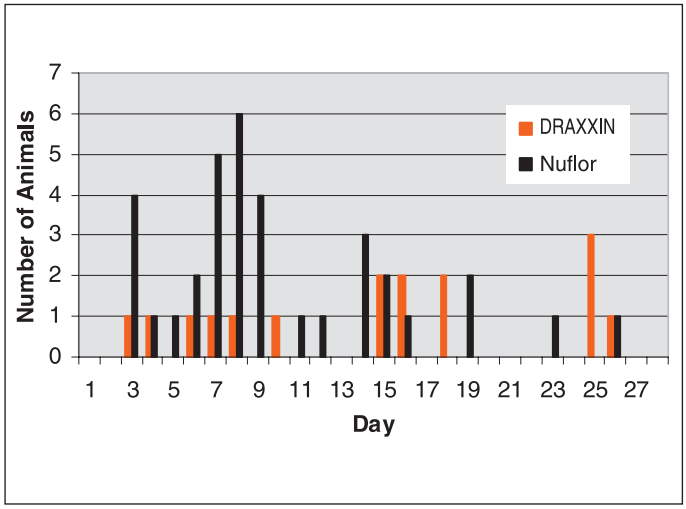


Figure 4b. Cumulative Distribution of Animals that Received Their 1st Re-treatment by Day, from Day 3 through Day 28; Treatment Study 2 (Colorado): DRAXXIN or Nuflor

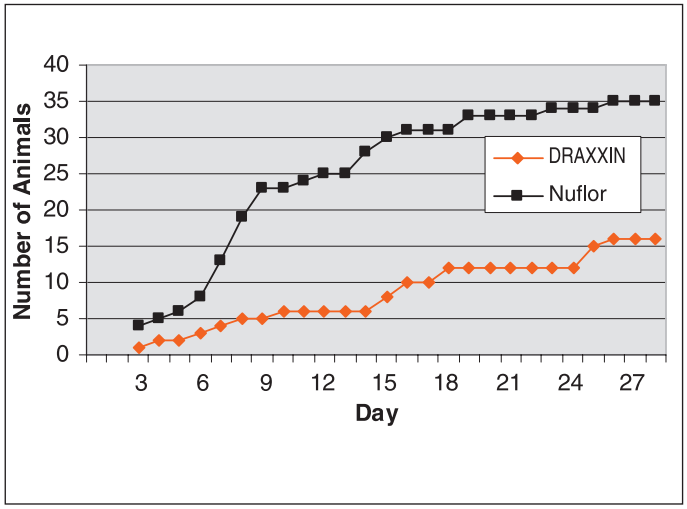


Table 5. Body Weight and Average Daily Gain for Animals that Remained in Treatment Study 2 (Colorado); DRAXXIN or Nuflor

	Initial Body Weight* (lb)			Final Body Weight (lb)		Average Daily Gain* (lb/day)		
Days	**DRAXXIN**	***P* Value**	**Nuflor**	**DRAXXIN**	**Nuflor**	**DRAXXIN**	***P* Value**	**Nuflor**
0-28	534.7	0.0858	512.9	612.6	588.9	2.78	0.7152	2.72
28-Re-implant**	612.6	0.0875	588.9	912.6	891.1	4.35	0.7931	4.38
Re-implant-Close†	912.6	0.2427	891.1	1176.4	1178.4	3.47	0.0054	3.78
0-Close	534.7	0.9240	512.9	1176.4	1178.4	3.71	0.1113	3.85

* Least-Squares Mean. Repeated measures mixed model least-squares means estimate of body weight and average daily gain did not include values for animals removed before day 28, or for mortalities or chronics removed prior to the day of re-implant or the day of harvest.
Note: Re-implant occurred on either day 97 or day 99 (mean=97).
† Close was on either day 173 or day 175 (mean=173).

Table 6. Carcass Adjusted Least-Squares Mean Final Body Weight, Weight Gain, Average Daily Gain and Hot Carcass Weight to Close* for Animals that Remained in Treatment Study 2 (Colorado); DRAXXIN or Nuflor, n (SEM)

	DRAXXIN	***P* Value**	**Nuflor**
Number of Animals	93		88
Final Body Weight, lb	1112.6 (15.13)	0.7473	1106.1 (15.54)
Weight Gain, lb	576.3 (10.60)	0.3290	591.2 (10.90)
Average Daily Gain, lb/day	3.33 (0.06)	0.3290	3.42 (0.06)
Hot Carcass Weight, lb	723.2 (9.83)	0.7473	718.9 (10.10)

* Chronics and mortalities removed.

2nd re-treatment with LA-200 (20 mg oxytetracycline/kg BW). Animals that met these re-treatment criteria and were at least 2 days post-treatment with LA-200 were classified as chronics, and removed from the study. Re-treatment criteria and regimens were re-initiated on day 29. Animals that were re-treated 3 times during days 3 through 28 or 3 times between day 29 and close were classified as chronics and removed from the study. All animals remaining in the study were harvested on days 173 to 175.

Results for Study 2

First-treatment success for cattle treated with DRAXXIN was significantly higher (P=0.002 for days 0 through 28, and P=0.009 for days 0 through close) than that for cattle treated with Nuflor (days 0 to 28: DRAXXIN, 82% and Nuflor, 64%; days 3 through close: DRAXXIN, 79.4% and Nuflor, 63.6%; Table 4). The frequency distribution of 1st re-treatments during days 3 to 28 (Figure 4a) revealed daily numerical differences for animals treated in each treatment group. Cumulative distribution of 1st re-treatments during days 3 to 28 (Figure 4b) revealed marked differences between treatment groups when the day-to-day variability of the frequency distribution accumulated. Overall, fewer animals that received first treatment with DRAXXIN required re-treatment than did those animals that received Nuflor. Removals due to BRD were not significantly different (P=0.058) for either treatment group during days 0 through 28, and for days 0 through close. The ADG was not significantly different for days 0 through 28 (P=0.7152), days 28 through day of re-implanting (P=0.7931), or days 0 through close (P=0.1113) for cattle ineither treatment group (Table 5). There were no significant differences (P>0.05) for final live body weights, hot carcass weights (Table 6) or individual carcass variables (kidney/pelvic/heart fat, fat thickness,

marbling score, carcass quality and yield grades after an overnight chill). Ribeye area for cattle treated with DRAXXIN (13.98 in2) was significantly larger (P=0.0396) than that for cattle treated with Nuflor (13.50 in2).

No adverse product-related experiences were reported.

Discussion

Bacteria isolated from clinically affected cattle prior to initial treatment during this study were consistent with those associated with BRD.[7,8] DRAXXIN is approved for treatment and control of BRD caused by *M haemolytica, H somni, P multocida* and *Mycoplasma bovis.*

DRAXXIN was more efficacious than was Nuflor, based on response to first treatment in both studies reported here. The substantial response to first treatment with DRAXXIN was followed by fewer re-treatments than for cattle that received Nuflor. That finding, in light of the different medications used for 1st and 2nd re-treatment, suggests that the choice of medication for first treatment had a major influence on response to subsequent treatment. Frequency distribution and cumulative distribution for 1st re-treatments should be considered when evaluating clinical response to treatment against BRD because they provide excellent, though different, views of the same information.

The number of BRD-associated removals (mortalities and chronics) was significantly (P<0.05) different for the 2 treatment groups in Study 1. In Study 2, the difference of BRD-associated removals for the 2 treatment groups was not significant at P=0.05 but was at P=0.058. That latter P value indicates that there was a 94.2% probability that the difference in BRD removals found in Study 2 was actually attributable to DRAXXIN.[9]

Re-treatment criteria were consistent within each phase of these studies, 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 were re-treated more than 3 times, throughout the course of the study, before they were classified as chronics and removed from the study. In 1 of the 2 studies reported here, ADG for animals that remained in the studies was greater for those treated with DRAXXIN than for those treated with Nuflor.

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.

Conclusion

Results of these treatment studies provide evidence that DRAXXIN administered as a single SC injection was safe and significantly more effective than was Nuflor for the treatment of undifferentiated BRD in cattle used in these studies. In both studies, DRAXXIN resulted in greater first-treatment success and lower BRD-associated removals (mortalities and chronics).

IMPORTANT SAFETY INFORMATION:
DRAXXIN has a pre-slaughter withdrawal time of 18 days. Do not use in female dairy cattle 20 months of age or older. Do not use in animals known to be hypersensitive to the product. See full Prescribing Information.

References

1 Nowakowski MA, Inskeep P, Risk J, et al. Pharmacokinetics and lung tissue concentrations of tulathromycin, a new triamilide antibiotic, in cattle. *Vet Ther* 2004;5:60-74.

2 Nutsch RG, Skogerboe TL, Rooney KA, Weigel DJ, Gajewski K, Lechtenberg KF. Comparative efficacy of tulathromycin, tilmicosin and florfenicol in the treatment of bovine respiratory disease in stocker cattle. *Vet Ther* 2005; in press.

3 Skogerboe TL, Rooney KA, Nutsch RG, Weigel DJ, Gajewski K, Kilgore WR. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. *Vet Ther* 2005; in press.

4 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.

5 First-treatment success = did not meet criteria for subsequent treatment, referred to as retreatment.

6 Chronic = received ≥3 re-treatments and removed from study.

7 Mosier DA. Bacterial pneumonia, bovine respiratory disease update. *Vet Clin North Am Food Anim Pract* 1997;13(3):483-493.

8 Woolums, AR, Ames TR, Baker JC.

Lower respiratory tract diseases. In: BP Smith, ed. *Large Animal Internal Medicine*, 4th ed. St. Louis, MO: Mosby, Inc; 2009; 601-643.

9 SAS. *SAS/STAT User's Guide*. Version 8. Cary, NC: SAS Institute Inc; 1999.

FULL PRESCRIBING INFORMATION FOR USE IN CATTLE ONLY

Draxxin®

(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) and veal calves. Not for use in female dairy cattle 20 months of age or older.

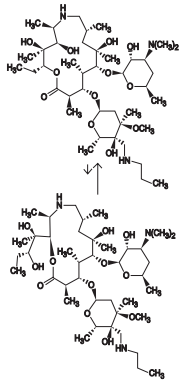
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

DRAXXIN Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of DRAXXIN 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.

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-hexopyrano-syl]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-azacy-clopentadecan-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 – DRAXXIN 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 – DRAXXIN Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis.*

Foot Rot – DRAXXIN 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 - DRAXXIN 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. 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

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. 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 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.

ADVERSE REACTIONS

Cattle

In one BRD 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.

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 a complete listing of adverse reactions for DRAXXIN (tulathromycin injection) Injectable Solution reported to the CVM see: http://www.fda.gov/AnimalVeterinary.

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 DRAXXIN 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 DRAXXIN 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 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 ($P \leq 0.05$) 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. Fifty-two DRAXXIN-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 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.

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 DRAXXIN to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with DRAXXIN. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of DRAXXIN 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, DRAXXIN 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 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. 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 DRAXXIN 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 DRAXXIN (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 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).

IBK – Two field studies were conducted evaluating DRAXXIN 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 DRAXXIN-treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less (P < 0.0001) in both studies for DRAXXIN-treated calves compared to saline-treated calves.

Foot Rot - The effectiveness of DRAXXIN 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 DRAXXIN (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 DRAXXIN-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). Use this product within 45 days of the first puncture and puncture a maximum of 20 times. If more than 20 punctures are anticipated, the use of automatic injection equipment of a repeater syringe 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

DRAXXIN Injectable Solution is available in the following package sizes:

- 50 mL vial
- 100 mL vial
- 250 mL vial
- 500 mL vial

NADA 141-244, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

To report a suspected adverse reaction or to request a safety data sheet call **1-888-963-8471**. 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.

For additional DRAXXIN product information call: **1-888-DRAXXIN** or go to **www.DRAXXIN.com**

TAKE TIME OBSERVE LABEL DIRECTIONS

Made in Spain

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