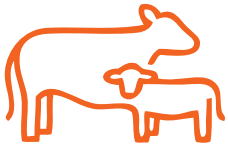
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TECHNICAL BULLETIN



Comparative Efficacy of DRAXXIN® vs Zuprevo® for First-Line Treatment of Acute BRD in Feedlot Heifers

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Parsippany, NJ 07054

Summary

- A study compared the health impacts of 2 macrolide antimicrobials when used for initial first-line treatment of naturally occurring acute BRD in feedlot heifers.[1]
  - 600 newly arrived heifers were randomly assigned to 2 treatment groups (n=300/group) as animals were diagnosed with clinical BRD over a 10-day period.
  - One group was treated with DRAXXIN® (tulathromycin) while the other group received Zuprevo® (tildipirosin). A 10-day post-treatment interval was observed during which no other BRD treatment was provided.
  - Both groups received identical non-macrolide medications for subsequent treatments, as needed.
- DRAXXIN generated an initial treatment success rate of 67.2%, significantly greater (P = 0.05) than the 59.3% success rate for the Zuprevo group (13.3% relative improvement over Zuprevo).
- A reduced percentage of heifers initially medicated with DRAXXIN needed retreatment (trend, P = 0.09), with fewer additional courses of therapy.
- BRD mortality was significantly reduced (P = 0.02) by 51% for cattle treated with DRAXXIN first-line therapy (5.0%) compared to Zuprevo (10.3%), which would provide substantial additional revenues at harvest for the DRAXXIN group.
- Study results confirmed that DRAXXIN continues to represent the reliable, cost-effective, and judicious first-line choice for BRD treatment protocols.

DRAXXIN® provided a greater rate of initial treatment success and cut BRD mortality by half compared to first-line treatment using Zuprevo®, thus producing additional revenues at harvest.

Feedyard managers and veterinarians continually search for better ways to lower the economic impacts of bovine respiratory disease (BRD) in their operations. One area of great interest and research involves the development and adjustment of antimicrobial strategies used to treat or control BRD. The advent of macrolide antimicrobials has been one of the major developments in BRD management and has greatly expanded the choice of available medications. Macrolides are often preferred for initial first-line therapy of sick cattle due to their excellent record of BRD resolution following a single treatment and reduction in BRD mortality. When subsequent medication is needed, an antimicrobial from a different chemical class is then used.

DRAXXIN® is a macrolide antimicrobial for the control and treatment of BRD that delivers a full course of therapy in a single dose.

600 feedlot heifers diagnosed with BRD were initially treated with either DRAXXIN® or Zuprevo,™ with identical non-macrolide medications used for retreats, as needed.

Because several newer-generation macrolide products have been introduced to the US beef industry, some feedlot professionals might presume they deliver equitable outcomes for BRD management. A comparative research study evaluated the health impacts of 2 macrolide products — DRAXXIN® (tulathromycin, Zoetis) or Zuprevo® (tildipirosin; Merck) — when used for first-line treatment of naturally occurring acute BRD in feedlot heifers.[1]

DRAXXIN® Overview

DRAXXIN Injectable Solution is an antimicrobial for the control and treatment of BRD that conveniently delivers a full course of therapy in a single dose. Tulathromycin is a semi-synthetic macrolide compound developed by Zoetis scientists as a highly bioavailable, long-acting antimicrobial for treatment of BRD.[2] Administered as a single subcutaneous (SC) injection at 1.1 mL/100 lb (2.5 mg/kg) body weight (BW), DRAXXIN is indicated for the treatment of BRD associated with 4 of the most common bacterial respiratory pathogens of cattle: *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis*. These indications make DRAXXIN particularly well-suited for initial first-line therapy of BRD, and for use in control programs for arriving feedlot cattle when animals are experiencing stress due to transport, commingling, etc., and are at high risk of BRD pathogen exposure. DRAXXIN is also indicated for treatment of infectious bovine keratoconjunctivitis associated with *Moraxella bovis*, and bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii.*

Experiment Design

The study involved 791 Angus-cross beef heifers averaging 516 lb BW that were trucked 15 hours from 3 sources in the southeastern US to a research feedlot in the Texas panhandle region during early/mid November. Though overall health of the calves was good at the time of arrival, shipping stress and commingling put the animals at high risk for development of BRD. Arriving over a 10-day period, heifers were placed on feed for a grow/finish period lasting through mid July (approximately 250 days). Cattle were processed within 24 hours of arrival according to standard procedures at the feedyard (vaccinated with BOVI-SHIELD GOLD® 5 and ULTRA CHOICE® 7, treated for internal and external parasites with DECTOMAX,® implanted with SYNOVEX® C, and administered LUTALYSE® to abort any pregnancies).

Beginning the day after arrival processing (day 0) and continuing for 10 days, heifers that exhibited clinical signs of BRD were assigned a clinical appearance score (CAS; animals rated using 5 categories, 0-4; 0=normal, 4=moribund). The criteria for enrollment in the study included a CAS of 1 and rectal temperature ≥ 104°F, or a CAS ≥ 2 regardless of temperature. A total of 600 clinically ill heifers were pulled for enrollment, weighed (average 503 lb BW), and randomly assigned to either of 2 treatment groups for first-line BRD treatment (Figure 1):

- Zuprevo 18%: 4.0 mg tildipirosin/kg BW (1 mL/100 lb), n=300;
- DRAXXIN: 2.5 mg tulathromycin/kg BW (1.1 mL/100 lb), n=300.

Treatments were injected as a single dose SC in the left lateral neck, and a 10-day post-treatment interval (PTI) was observed during which no other BRD treatment was provided. Enrolled heifers were allocated to 12 commingled home pens after receiving first-line treatment, with each pen holding 50 head, 25 of each treatment group.

After the initial PTI period elapsed, heifers again demonstrating signs of BRD (same criteria as before) were pulled and retreated

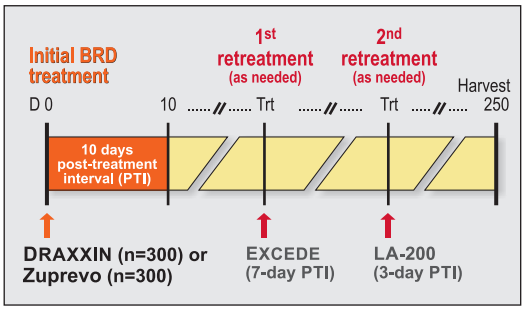


Figure 1 – Study design.

using the following sequenced regimen of non-macrolide products, as needed:

- 1st retreatment: EXCEDE® (6.6 mg ceftiofur/kg BW) administered SC at the base of the ear, with a 7-day PTI before additional intervention;
- 2nd retreatment: LIQUAMYCIN® LA 200® (9.0 mg oxytetracycline/lb BW) administered SC in the neck, with a 3-day PTI before additional intervention;
- heifers needing a 3rd retreatment were considered a BRD chronic, weighed, removed from the pen, and excluded from performance assessments.

Any animal showing a CAS of ≥ 3 during a PTI period was administered emergency therapy and removed from the study, and any heifer with a CAS of 4 was humanely euthanized. Feedyard personnel making clinical observations did not have knowledge of treatment group assignments (masked to treatment).

Cattle were fed standard feedlot rations (including monensin and tylosin) formulated to meet or exceed requirements for their class and weight. ACTOGAIN™ (ractopamine, 350 mg/hd/d) was included in finish rations for the last 35 days prior to harvest (no withdrawal period needed). Ration changes occurred according to facility procedures and water was provided ad libitum. After 90 days on feed (DOF), cattle were weighed and re-implanted (SYNOVEX® ONE FEEDLOT). Heifers were also weighed at study conclusion (~day 250, mid July) and when any treatments were administered.

Clinical BRD parameters assessed during the study included rates of first-treatment success (defined as no additional BRD treatment needed), 1st and 2nd retreatment success, chronics, removals (some of which later died), and mortalities (cause confirmed by necropsy). Average daily gain (ADG) was also measured (deads/removals-out basis). Animals that were removed prior to being eligible for another treatment and subsequently did not die of BRD (n=9) were not considered either a treatment failure or success.

Collected data were statistically analyzed using appropriate standard methods. Each animal comprised an experimental unit for all parameters measured. Significance between treatments was declared at $P \leq 0.05$.

Results

Study outcomes summarized in Table 1 and Figure 2 show that first-line initial treatment with DRAXXIN provided superior BRD resolution compared to Zuprevo. Heifers treated with DRAXXIN demonstrated an excellent initial treatment success rate of 67.2% (no subsequent BRD development), an outcome significantly greater ($P = 0.05$) than the 59.3% success rate observed for the Zuprevo group. In terms of relative improvement, the DRAXXIN success rate was **13.3%** better than that achieved by Zuprevo.

DRAXXIN® improved initial treatment success rate 13.3% compared to Zuprevo®.

Greater initial treatment success means less need for retreatment (judicious use implications), and a statistical trend in that direction ($P = 0.09$) was detected as DRAXXIN reduced the percentage of cattle retreated following initial treatment (Figure 2). No differences between treatment groups ($P \geq 0.47$) were detected for success rates of 1st and 2nd retreatments or for the rate of chronics, though a numerical advantage for DRAXXIN was noted for each parameter.

DRAXXIN® reduced the percentage of cattle retreated following initial treatment.

Cattle receiving DRAXXIN first-line therapy demonstrated significantly ($P = 0.02$) reduced rates of BRD mortality compared to animals initially treated with Zuprevo

Table 1 – Mean responses of feedlot heifers to BRD treatment.

Item	Zuprevo	DRAXXIN	*P* value
Initial treatment success, % (n)[a]	59.3 (174)	67.2 (197)	0.05
Cattle retreated, % (n)[b]	34.4 (104)	28.0 (85)	0.09
1st retreatment success, % (n)[a]	53.3 (54)	55.3 (46)	0.79
2nd retreatment success, % (n)[a]	33.3 (15)	38.5 (15)	0.62
Chronics, % (n)[a]	14.0 (45)	12.0 (39)	0.47
Removals (all causes), % (n)	19.2 (59)	14.9 (46)	0.16
BRD mortality, % (n)	10.3 (31)	5.0 (15)	0.02
Re-implant average daily gain, lb[c]	3.09	3.18	0.20
Final average daily gain, lb	3.19	3.20	0.85

[a] Treatment success defined as not requiring further treatment for BRD and not euthanized/died of BRD (or removed as a chronic that was treated 3 times and then removed). Animals removed prior to eligibility for another treatment and not subsequently dying of BRD (n=9), or were treatment deviations (n=1), were not considered either a failure or success (missing data points for analysis).
[b] Not including deads/removals.
[c] Heads counts were 256/241 at re-implant and 251/238 at close-out for Draxxin/Zuprevo groups, respectively. Re-implant at 90 DOF.

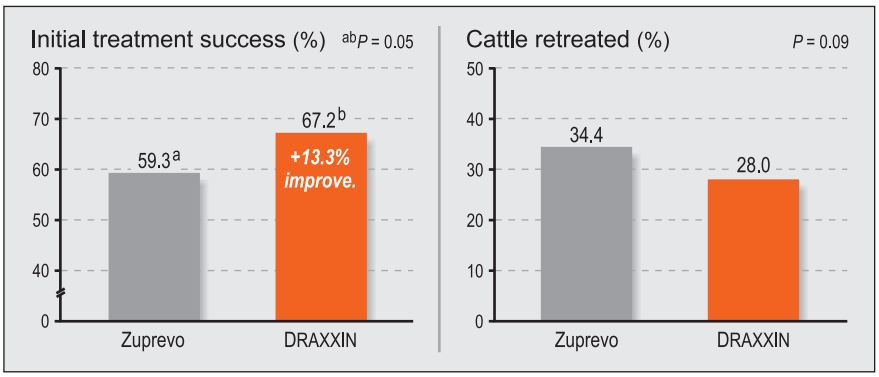


Figure 2 – Rates of first-line treatment success and cattle needing retreatment.

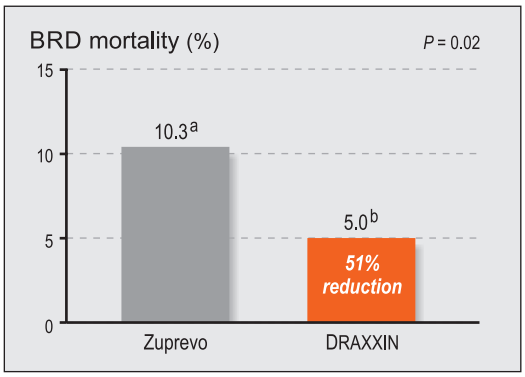


Figure 3 – BRD mortality rate during the entire 250-day feeding period.

BRD mortality fell 51% for cattle treated with DRAXXIN,® so more animals survived to harvest and generated income.

(Figure 3). BRD mortality over the study course averaged 5.0% in the DRAXXIN group, a **51%** relative reduction compared to the 10.3% BRD death rate for heifers in the Zuprevo group. The substantial revenue generated at harvest by 16 additional live animals (average 1282 lb BW) in the DRAXXIN group offers strong implication of an additional significant economic benefit favoring the DRAXXIN protocol.

All cattle that were removed from the study were followed for determination of final disposition. Of 46 cattle that were treated with DRAXXIN and removed:

- 15 subsequently died of BRD (13 removed during the PTI, avg. 6.7 DOF; 2 removed after the PTI, avg. 36 DOF);
- 31 were eventually turned out on wheat (4 removed during the PTI, avg. 6.7 DOF; 27 removed after the PTI, avg. 39 DOF).

Of 59 cattle that were treated with Zuprevo and removed:

- 31 subsequently died of BRD (17 removed during the PTI, avg. 5.8 DOF; 14 removed after the PTI, avg. 23 DOF);
- 28 were eventually turned out on wheat (5 removed during the PTI, avg. 5.6 DOF; 23 removed after the PTI, avg. 30 DOF).

No significant differences in ADG were detected between treatment groups at re-implant or harvest (Table 1, $P \geq 0.20$).

DRAXXIN® continues to represent a reliable, cost-effective, and judicious first-line choice for BRD treatment protocols.

Conclusions

Results of this study confirmed that use of DRAXXIN for initial first-line therapy of BRD in feedlot heifers provided superior disease resolution relative to Zuprevo. DRAXXIN significantly improved first treatment success rate and reduced BRD mortality compared to Zuprevo, and demonstrated a trend toward reduction in the percentage of cattle retreated following initial treatment. Heifers treated with DRAXXIN required fewer subsequent antimicrobial treatment courses compared to cattle medicated with Zuprevo, and helped more cattle survive to market and thus generate harvest revenues.

DRAXXIN continues to represent a reliable, cost-effective, and judicious first-line choice for BRD treatment protocols, helping optimize the health and profitability of feedlot cattle afflicted with BRD.

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

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.

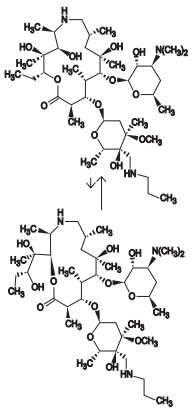
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

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

INDICATIONS

Beef and Non-Lactating Dairy Cattle

BRD – 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

Revised: June 2018

References

1. Data on file, Study Report No. 16CRGAIF-01-02, Zoetis Inc.
2. Evans NA. Tulathromycin: an overview of a new triamilide antibiotic for livestock respiratory disease. *Vet Ther* 2005; 6:83-95.

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