ABSTRACT

Six hundred calves identified with BRD by feedyard pen riders were presented for further evaluation to a hospital facility. Calves that met the following criteria as determined by a veterinarian were randomly allocated to receive either Zuprevo® or Draxxin® to evaluate the clinical efficacy of these compounds for the treatment of naturally occurring BRD: a rectal temperature ≥ 104.0°F (≥ 40°C), no previous treatments for disease and no signs referable to disease of other organ systems. Eligible lots contained calves in two different risk categories: low or moderate risk of developing BRD that did not receive a metaphylactic antimicrobial at arrival and calves suspected to be at high risk of developing BRD that received a metaphylactic antimicrobial (tilmicosin) at feedlot arrival. After allocation, treated calves were returned to their home pen(s) and followed for 60 days. All enrolled animals that died during the study were gross necropsied by a veterinarian or trained feedlot personnel. There were no differences (P > 0.12) in health outcomes between calves that received Zuprevo versus those that received Draxxin. Additionally, there were no differences in first treatment success or case fatality risk based on metaphylaxis status (P = 0.54 and 0.95, respectively). Tildipirosin is an effective antimicrobial for first treatment of BRD in medium- to low-risk populations of cattle as compared with tulathromycin. This population represents the largest proportion of animals placed on feed in U.S. feedlots.

INTRODUCTION

Zuprevo is an antimicrobial medication indicated for treatment and control of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni. When administered according to the label dose of 1 mL/100 lbs. of body weight (BW), tildipirosin is rapidly absorbed, distributes widely and provides concentrations in bovine lungs for an extended period. This study was performed to compare the clinical efficacy of Zuprevo with Draxxin in the treatment of naturally occurring BRD. The conditions were typical of commercial feedlots and reflective of the majority of cattle placed in U.S. feedlots.
RESULTS AND DISCUSSION

A total of 600 calves were enrolled into the study (Zuprevo = 299; Draxxin = 301) from an at-risk pool of 58,178 animals eligible during the enrollment phase. A total of seven removals occurred throughout the study. The cause for removal and numbers within the treatment group were as follows: two bloats and two heart failures in the Zuprevo treatment group and one calf died due to thromboembolic meningoencephalitis, one calf died due to atypical interstitial pneumonia and one calf with musculoskeletal injury during re-implant in the Draxxin treatment group. None of the removals were associated with treatments being evaluated based upon the investigator’s evaluation.

Animal Enrollment: Calves were observed daily by pen riders for identification of BRD based upon subjective evaluation including appearance, attitude, gauntness, nasal discharge and reluctance to move. When calves presented these signs, they were pulled from home pens and moved to the hospital for confirmatory diagnosis. A veterinarian used the following criteria for study inclusion: in pen signs as reported by the pen riders, a rectal temperature of ≥ 104°F, no previous treatment for disease, lot cohorts with ≥ 60 days estimated to harvest, and absence of clinical signs referable to disease in other organ systems. Animals from eligible lots that did not receive an antibiotic at arrival processing were enrolled at any time. Animals from lots that did receive an arrival antibiotic, tilmicosin (Micotil, Elanco Animal Health, Greenfield, IN; 13.2 mg/kg of body weight (BW) subcutaneously (SC); 2.0 mL/100 lbs. of BW) for control of BRD, were not eligible until ≥ 21 days post metaphylaxis.

Upon meeting the inclusion criteria, calves were randomly assigned to one of two treatment groups by lot of origin: either tildipirosin (Zuprevo, Merck Animal Health, Whitehouse Station, NJ; 1 mL/100 lbs. of body weight subcutaneously in left neck) or tulathromycin (Draxxin, Zoetis Animal Health, Parsippany, NJ; 1.1 mL/100 lbs. of body weight subcutaneously in left neck). Calves were enrolled in a 1:1 ratio within origin lot, identified with duplicate ear tags with both body weight and rectal temperature measured and recorded in a feedlot computer system. Initial weight at enrollment was 801.2 (SE 10.15) with no difference (P = 0.71) noted between those receiving Zuprevo and those receiving Draxxin as initial BRD treatment. Post-allocation, calves were evaluated for 60 days to monitor subsequent health outcomes.

BRD Retreatments: Calves were eligible for retreatment after a five-day post-treatment interval (PTI) was imposed for both Zuprevo and Draxxin. Pen riders, who were masked to experimental treatment, identified cattle that had met or exceeded the PTI, expressed signs of BRD morbidity and (or) had the appearance of lost body weight since first treatment as candidates in need of removal to a hospital for further evaluation. A rectal temperature ≥ 104 °F was used to confirm a BRD diagnosis. Calves requiring a second treatment for BRD were administered florfenicol (Nuflor®, Merck Animal Health, Whitehouse Station, NJ; 6 mL/100 lbs. of body weight subcutaneously). A three-day PTI was used after the second treatment for BRD. Calves which required a third treatment for BRD were administered enrofloxacin (Baytril®, Bayer Animal Health, Shawnee, KS; 4.5 mL/100 lbs. of body weight subcutaneously). There were no animals that required additional treatment.

Feed, Housing and Water: Calves were fed diets formulated to meet or exceed NASEM (2016) maintenance requirements and were equal across treatment groups.

Statistical Analyses: Continuous outcomes (enrollment body weight and additional weights, enrollment rectal temperature and additional temperatures, and treatment death interval) were evaluated with linear mixed models. Binary outcomes (treatment successes and risk of case fatality) were evaluated using generalized logistic regression models. All models included a fixed effect for treatment group and random effects for lot of origin. Differences exhibiting a P value ≤ 0.05 were considered statistically significant. Additional models included fixed effect of treatment group; lots administered a metaphylactic antibiotic, treatment by metaphylaxis interaction and random effect for lot of origin. Models evaluating body weight, rectal temperature and treatment success at third treatment would not converge when constructed as described; therefore, the random effect for origin lot was removed from these models.

RESULTS AND DISCUSSION

A total of 600 calves were enrolled into the study (Zuprevo = 299; Draxxin = 301) from an at-risk pool of 58,178 animals eligible during the enrollment phase. A total of seven removals occurred throughout the study. The cause for removal and numbers within the treatment group were as follows: two bloats and two heart failures in the Zuprevo treatment group and one calf died due to thromboembolic meningoencephalitis, one calf died due to atypical interstitial pneumonia and one calf with musculoskeletal injury during re-implant in the Draxxin treatment group. None of the removals were associated with treatments being evaluated based upon the investigator’s
No health differences were identified in calves treated with Zuprevo compared to Draxxin for first treatment of BRD. Zuprevo is an effective antimicrobial for first treatment of BRD in the medium- to low-risk populations of cattle which represent the largest proportion of cattle on feed in the United States. No differences in health outcomes were identified in the population that received a macrolide on arrival for control of BRD followed by a macrolide for treatment of BRD when the interval between metaphylaxis and first pull BRD treatment was ≥ 21 days on feed.

There were no interactions (P>0.11) between treatment group and metaphylaxis status for health outcomes (data not shown). Rectal temperature at enrollment was 0.17°F greater (P=0.02) for no metaphylaxis cattle and 0.54°F greater (P=0.02) at third treatment for BRD for cattle that received metaphylaxis versus those that did not. The clinical significance of the rectal temperature at these times is unknown. It would seem highly unlikely that differences in rectal temperature at the time of first BRD pull, 21 days or greater after metaphylaxis, are the result of metaphylaxis administration. Differences in health outcome for cattle pulled for BRD and treated with Zuprevo or Draxxin were unremarkable (Table 1). First pull treatment success was 80.72% and 80.59% for cattle treated with Zuprevo or Draxxin, respectively (P=0.97). Third-pull treatment success was highly variable compared with first- and second-pull successes but not different (P=0.12) between BRD treatments. Case fatality risk percentage averaged 6.05% with no difference (P=0.89) between antibiotics used for first pull treatment. Rectal temperatures at the time of enrollment, second BRD treatment or third BRD treatment were not different (P>0.62) due to Zuprevo or Draxxin administration. Mean days to death after initial BRD treatment was different.

CONCLUSIONS
No health differences were identified in calves treated with Zuprevo compared to Draxxin for first treatment of BRD. Zuprevo is an effective antimicrobial for first treatment of BRD in the medium- to low-risk populations of cattle which represent the largest proportion of cattle on feed in the United States. No differences in health outcomes were identified in the population that received a macrolide on arrival for control of BRD followed by a macrolide for treatment of BRD when the interval between metaphylaxis and first pull BRD treatment was ≥ 21 days on feed.

ZUPREVO IMPORTANT SAFETY INFORMATION: FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. TO AVOID ACCIDENTAL INJECTION, DO NOT USE IN AUTOMATICALLY POWERED SYRINGES WHICH HAVE NO ADDITIONAL PROTECTION SYSTEM. IN CASE OF HUMAN INJECTION, SEEK MEDICAL ADVICE IMMEDIATELY AND SHOW THE PACKAGE INSERT OR LABEL TO THE PHYSICIAN. DO NOT USE Zuprevo® 18% IN SWINE. Fatal adverse events have been reported following the use of tildipirosin in swine. NOT FOR USE IN CHICKENS OR TURKEYS. Cattle intended for human consumption must not be slaughtered within 21 days of the last treatment. Do not use in female dairy calf 20 months of age or older. Use of this drug product in these cattle may cause milk residues. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal. The effects of Zuprevo® 18% on bovine reproductive performance, pregnancy and lactation have not been determined. Swelling and inflammation, which may be severe, may be seen at the injection site after administration. Subcutaneous injection may result in local tissue reactions which persist beyond slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

NUFLOR IMPORTANT SAFETY INFORMATION: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.
Table 1 Model-adjusted least square means (± SE) of health outcomes for first treatment of (BRD) by treatment group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Zuprevo</th>
<th>Draxxin</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head enrolled</td>
<td>295</td>
<td>298</td>
<td>-</td>
</tr>
<tr>
<td>Treatment success¹, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>80.72 (2.42)</td>
<td>80.59 (02.44)</td>
<td>0.97</td>
</tr>
<tr>
<td>Second</td>
<td>64.46 (7.30)</td>
<td>70.20 (07.49)</td>
<td>0.58</td>
</tr>
<tr>
<td>Third¹²</td>
<td>27.27 (13.43)</td>
<td>62.50 (17.12)</td>
<td>0.12</td>
</tr>
<tr>
<td>BRD case fatality risk, %</td>
<td>6.17 (1.95)</td>
<td>5.93 (1.95)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

¹ Treatment success defined as not requiring additional treatment for BRD and not dying within the 60-day monitoring period due to BRD.
² Third treatment outcomes did not include random effect for origin lot as no lots had multiple observations in calves treated three times.
*P-value displayed is main effect of treatment group. Model included random effect for origin lot.

Table 2 Model-adjusted least square means (± SE) of health outcomes for first treatment of BRD in calves stratified by rectal temperature.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&lt; 104.5°F</th>
<th>≥ 104.5°F</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head enrolled</td>
<td>302</td>
<td>291</td>
<td>-</td>
</tr>
<tr>
<td>First treatment successes¹,%</td>
<td>84.52 (2.23)</td>
<td>76.71 (2.60)</td>
<td>0.02</td>
</tr>
<tr>
<td>BRD second treatment, %</td>
<td>11.59 (1.84)</td>
<td>17.18 (2.21)</td>
<td>0.05</td>
</tr>
<tr>
<td>BRD case fatality risk, %</td>
<td>4.29 (1.55)</td>
<td>7.87 (2.35)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

¹ Treatment success defined as not requiring additional treatment for or dying from BRD within the 60-day monitoring period.
*P-value displayed is main effect of rectal temperature stratification; model included random effect for origin lot.

END NOTES

a R Studio Team 2016, Boston, MA
b Micotil®, Elanco Animal Health, Greenfield, IN
c Zuprevo®, Merck Animal Health, Whitehouse Station, NJ
d Draxxin®, Zoetis Animal Health, Parsippany, NJ
e Animal Management System, Animal Health International, Greeley, CO
f Nuflor®, Merck Animal Health, Whitehouse Station, NJ
g Baytril®, Bayer Animal Health, Shawnee, KS

REFERENCES


**TILDIPRISIN**

Injectable Solution for Cattle

**ANTIMICROBIAL DRUG:** 100 mg of tildipirosin/ml

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

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

**DESCRIPTION:** Zuprevo™ 18% is a ready-to-use sterile injectable solution containing tildipirosin, a semi-synthetic macrolide antibiotic. Each mL of Zuprevo 18% contains 180 mg of tildipirosin as the free base, 82.5 mg citric acid monohydrate, and monopotassium phosphate (400 mg phosphate ion), and water up to a final concentration adjusted to pH 5.5.

**CHEMICAL NOMENCLATURE AND STRUCTURE:** Tildipirosin is the nonproprietary name for (4R,5S,6S,7R,9R,15R,16R)-6-(4-Dimethylamino-3,5-dihydroxy-6-methyl-2-(tetrahydro-2H-pyran-2-yl)-4H-furo[3,4-b]pyran-5,9,13-trisubstituted-11H,13-diene-2,10-dione. The chemical structure of tildipirosin is shown below.

**INDICATIONS:** Zuprevo 18% is indicated for the treatment of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in beef and non-lactating dairy cattle, and for the control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with M. haemolytica, P. multocida, and H. somni.

**DOSAGE AND ADMINISTRATION:** Inject subcutaneously as a single dose in the neck at a dosage of 4 mg/kg BW in the neck:

- **Mannheimia haemolytica**
- **Pasteurella multocida**
- **Histophilus somni**

**H. somni**

**INDICATIONS:** Zuprevo™ 18% is a ready-to-use sterile injectable solution containing tildipirosin, a semi-synthetic macrolide antibiotic. Each mL of Zuprevo 18% contains 180 mg of tildipirosin as the free base, 82.5 mg citric acid monohydrate, and monopotassium phosphate (400 mg phosphate ion), and water up to a final concentration adjusted to pH 5.5.

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- **Pasteurella multocida**
- **Histophilus somni**

**H. somni**

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**CHEMICAL NOMENCLATURE AND STRUCTURE:** Tildipirosin is the nonproprietary name for (4R,5S,6S,7R,9R,15R,16R)-6-(4-Dimethylamino-3,5-dihydroxy-6-methyl-2-(tetrahydro-2H-pyran-2-yl)-4H-furo[3,4-b]pyran-5,9,13-trisubstituted-11H,13-diene-2,10-dione. The chemical structure of tildipirosin is shown below.

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Injectable Solution 300 mg/mL

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

Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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

DESCRIPTION NUFLOR Injectable Solution is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile NUFLOR Injectable Solution contains 300 mg of florfenicol, 250 mg N-Methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol 400. The chemical name for florfenicol is 2,2-Dichloro-N-[1-(fluoromethyl)-2-hydroxy-2-(4-ethylthiofuran-2-yl)acetamide.

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

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

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

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

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

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

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

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

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Residues in edible tissue, including milk, from animals treated with NUFLOR Injectable Solution are not a concern for human consumption. A 1X, 3X, and 5X safety study was conducted in feeder calves. Two intramuscular injections of 300 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 10X safety study was conducted in healthy cattle to evaluate effects of NUFLOR Injectable Solution administration at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, NUFLOR Injectable Solution administration had no long-term effect on body weight, rate of gain, or feed conversion.

STORAGE INFORMATION Store between 2°-30°C (36°-86°F). Refrigeration is not required.

HOW SUPPLIED NUFLOR Injectable Solution is packaged in 100 mL (NDC 0061-1116-04), 250 mL (NDC 0061-1116-05), and 500 mL (NDC 0061-1116-06) glass sterile multiple-dose vials.


[Rev. 02/2018]