Canadian commercial feedlot study\(^1\) comparing Zuprevo™ to Draxxin® and Micotil® when used on arrival in calves at high risk of developing BRD

**SUMMARY**

A commercial field study was conducted in Alberta to evaluate Zuprevo, Draxxin and Micotil when used for on-arrival treatment in high-risk calves. Health outcomes and feedlot performance to close-outs and carcass characteristics were compared.

There were no significant differences between calves treated with Zuprevo or Draxxin on all health and performance outcomes. Compared to Micotil-treated calves the Zuprevo group had a significantly lower first pull rate, lower overall mortality and a lower mortality due to histophilosis.

Also, Zuprevo-treated calves had significantly higher Yield Grade 1 carcasses and lower Yield Grade 2 carcasses than did Draxxin- or Micotil-treated calves.

Based on the results of this study, Zuprevo is more efficacious than Micotil and comparable to Draxxin, when administered as on-arrival therapy in feedlot calves at high risk of developing respiratory disease.

**OBJECTIVE**

The study was conducted to evaluate the relative effect of Zuprevo on animal health, feedlot performance and carcass characteristic outcomes, when used as an on-arrival therapy in feedlot calves at high risk of developing BRD.

**MATERIALS AND METHODS**

- Auction mart-sourced, exotic crossbred calves from western Canada were used in the study. Approximately 10,000 calves weighing 400-700 lb with predicted high risk of developing BRD were enrolled. Two study sites in Alberta were used (3 replicates per site). The animals were managed using the standard implant, vaccination, individual animal management, and pre-marketing feeding procedures determined by the investigators. The procedures used were standardized and applied to the three experimental groups at both sites.

- Each animal was uniquely identified with a CCIA RFID tag and a feedlot management tag, applied at processing. All identification tags were cross-referenced in the animal health software system. Feedlot processing included: vaccination against infectious bovine rhinotracheitis, bovine viral diarrhea, bovine respiratory syncytial virus, parainfluenza virus, *Histophilus somni*, *Mannheimia haemolytica* and clostridiosis, as well as administration of a pour-on endectocide.

- The calves were randomly allocated to one of the three experimental groups based upon the randomization table provided by the investigator. The animals assigned to each experimental group were housed in separate multi-pen lots, and sets of multi-pen lots were built sequentially until there were six replicates. Each replicate contained one multi-pen lot (508-620 head in two pens) for each experimental group.

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\(^1\)Data on file: S11414-00-MCR-CLI-RM, final report (November 26, 2012).

**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 AUTOMATICALLYPOWERED 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 cattle 20 months of age or older. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal. The effects 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.
### Treatment groups:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Head Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuprevo</td>
<td>1 mL/100 lb (4 mg/kg)</td>
<td>3,358</td>
</tr>
<tr>
<td>Draxxin</td>
<td>1.1 mL/100 lb (2.5 mg/kg)</td>
<td>3,359</td>
</tr>
<tr>
<td>Micotil</td>
<td>1.5 mL/100 lb (10 mg/kg)</td>
<td>3,356</td>
</tr>
</tbody>
</table>

Calves were housed in 250- or 300-head capacity, open-air, dirt-floor pens with concrete fence line feed bunks typical of feedlots in western Canada.

Pens were observed at least once a day by experienced pen checkers. Animals deemed sick were moved to a hospital facility for assessment. Animal health personnel were blinded as to the experimental status of each pen.

A diagnosis of “undifferentiated fever” (UF) was made if:

- there was an absence of abnormal clinical signs referable to organ systems other than the respiratory tract,
- the calf had an elevated rectal temperature > 40.5°C (≥105.0°F),
- there was no previous treatment history for no fever (NF), and
- a period of at least three days had elapsed since allocation-and-arrival metaphylactic treatment.

UF relapses were defined as calves returned to their original feedlot pen following initial UF therapy that were subsequently selected as “sick” by the pen checkers and exhibited respiratory signs.

A diagnosis of “no fever” (NF) was made if:

- there was an absence of abnormal clinical signs referable to organ systems other than the respiratory tract,
- the calf had an elevated rectal temperature > 40.5°C (≥105.0°F),
- there was no previous treatment history for NF, and
- a period of at least three days had elapsed since allocation-and-arrival metaphylactic treatment.

NF relapses were defined as calves returned to their original feedlot pen following initial UF therapy that were subsequently selected as “sick” by the pen checkers and exhibited respiratory signs.

The treatment protocols used for UF and NF were identical and standardized for all experimental groups. Other diseases were treated and recorded as per the standard feedlot protocol.

All animals that died were examined post mortem. The cause of death was determined for each animal by a veterinarian, based on the findings of the gross post-mortem examination.

Animals from the experimental groups in each replicate were slaughtered on an equal days-on-feed basis.

Zuprevo 1 mL/100 lb (4 mg/kg), 3,358 head
Draxxin 1.1 mL/100 lb (2.5 mg/kg), 3,359 head
Micotil 1.5 mL/100 lb (10 mg/kg), 3,356 head
Results

Health Outcomes

There were no statistical differences between Zuprevo and Draxxin in the health outcomes. However, Zuprevo-treated calves had a significantly lower first UF treatment rate, lower overall mortality and fewer death losses due to histophilosis than did Micotil-treated calves.

<table>
<thead>
<tr>
<th>Animal Health Variable Morbidity</th>
<th>Zuprevo</th>
<th>Draxxin</th>
<th>Micotil</th>
<th>P-value Zuprevo vs. Draxxin</th>
<th>P-value Zuprevo vs. Micotil</th>
</tr>
</thead>
<tbody>
<tr>
<td>First UF Treatment</td>
<td>7.00%</td>
<td>7.02%</td>
<td>15.07%</td>
<td>0.918</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First UF Relapse</td>
<td>23.16%</td>
<td>20.66%</td>
<td>23.70%</td>
<td>0.568</td>
<td>0.971</td>
</tr>
<tr>
<td>First NF Treatment</td>
<td>4.36%</td>
<td>3.75%</td>
<td>5.38%</td>
<td>0.365</td>
<td>0.202</td>
</tr>
<tr>
<td>First NF Relapse</td>
<td>20.05%</td>
<td>17.44%</td>
<td>22.03%</td>
<td>0.221</td>
<td>0.657</td>
</tr>
<tr>
<td>Chronicity†</td>
<td>3.05%</td>
<td>2.49%</td>
<td>3.13%</td>
<td>0.226</td>
<td>0.809</td>
</tr>
<tr>
<td>Wastage‡</td>
<td>2.31%</td>
<td>2.01%</td>
<td>2.45%</td>
<td>0.499</td>
<td>0.688</td>
</tr>
</tbody>
</table>

†Chronicity is the number of animals with chronic disease (all causes) divided by the number of animals allocated.
‡Wastage is the number of animals with chronic disease (all causes) that did not die divided by the number of animals allocated.
Performance Outcomes and Carcass Traits

Health Outcomes

There were no statistical differences between Zuprevo and Draxxin in the health outcomes. However, Zuprevo-treated calves had a significantly lower first UF treatment rate, lower overall mortality and fewer death losses due to histophilosis than did Micotil-treated calves.

<table>
<thead>
<tr>
<th>Feedlot Performance Variable</th>
<th>Zuprevo</th>
<th>Draxxin</th>
<th>Micotil</th>
<th>Standard Error</th>
<th>P-value Zuprevo vs. Draxxin</th>
<th>P-value Zuprevo vs. Micotil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Daily Gain (lb/day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Weight Basis</td>
<td>3.13</td>
<td>3.14</td>
<td>3.13</td>
<td>±0.03</td>
<td>0.685</td>
<td>0.960</td>
</tr>
<tr>
<td>Carcass Weight Basis</td>
<td>3.26</td>
<td>3.27</td>
<td>3.26</td>
<td>±0.02</td>
<td>0.788</td>
<td>0.956</td>
</tr>
<tr>
<td><strong>Dry Matter Intake to Gain Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Weight Basis</td>
<td>6.41</td>
<td>6.48</td>
<td>6.44</td>
<td>±0.06</td>
<td>0.162</td>
<td>0.595</td>
</tr>
<tr>
<td>Carcass Weight Basis</td>
<td>6.16</td>
<td>6.20</td>
<td>6.19</td>
<td>±0.03</td>
<td>0.325</td>
<td>0.494</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carcass Variable</th>
<th>Zuprevo</th>
<th>Draxxin</th>
<th>Micotil</th>
<th>Standard Error</th>
<th>P-value Zuprevo vs. Draxxin</th>
<th>P-value Zuprevo vs. Micotil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yield Grades</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yield Grade 1</td>
<td>71.98%</td>
<td>67.73%</td>
<td>68.40%</td>
<td>±2.23%</td>
<td>0.003</td>
<td>0.009</td>
</tr>
<tr>
<td>Yield Grade 2</td>
<td>22.06%</td>
<td>25.32%</td>
<td>25.68%</td>
<td>±1.74%</td>
<td>0.013</td>
<td>0.008</td>
</tr>
<tr>
<td>Yield Grade 3</td>
<td>5.95%</td>
<td>6.95%</td>
<td>5.92%</td>
<td>±0.64%</td>
<td>0.155</td>
<td>0.959</td>
</tr>
<tr>
<td><strong>Dry Matter Intake to Gain Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prime</td>
<td>0.19%</td>
<td>0.21%</td>
<td>0.12%</td>
<td>±0.05%</td>
<td>0.765</td>
<td>0.404</td>
</tr>
<tr>
<td>AAA</td>
<td>37.38%</td>
<td>41.01%</td>
<td>40.07%</td>
<td>±2.09%</td>
<td>0.102</td>
<td>0.212</td>
</tr>
<tr>
<td>AA</td>
<td>58.21%</td>
<td>55.10%</td>
<td>55.61%</td>
<td>±1.82%</td>
<td>0.107</td>
<td>0.170</td>
</tr>
<tr>
<td>A</td>
<td>3.38%</td>
<td>2.46%</td>
<td>3.15%</td>
<td>±0.56%</td>
<td>0.073</td>
<td>0.631</td>
</tr>
</tbody>
</table>

Health Outcomes

Zuprevo is the newest long-acting macrolide product on the market for the reduction of morbidity, when administered on arrival to feedlot calves at high risk of developing bovine respiratory disease. In this study, Zuprevo is proven to be effective.
(Tildipirosin)
Injectable Solution for Cattle

ANTIMICROBIAL DRUG:
180 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 or in 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 semisynthetic macrolide antibiotic. Each mL of Zuprevo 18% contains 180 mg of tildipirosin as the free base, 82.5 mg citric acid monohydrate and 400 mg propylene glycol, and water up with citric acid monohydrate added to adjust pH.

CHEMICAL NOMENCLATURE AND STRUCTURE: Tildipirosin is the nonproprietary name for (1R,13E)-14R,56,6S,7R,9R,15R,16R-6-(4-Dimethylamino-3,5-dihydroxy-6-methyl-tetrahydro-pyran-2-yl)-16-ethyl-4-hydroxy-5,9,13-trimethyl-7-(2-piperidin-1-yl-ethyl)-15-piperidin-1-yl-methyl-oxacycloheptadecane-11,13-diene-2,10-dione. The empirical formula is C₃₆H₅₅NO₅. 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 (1 mL/100 lb. body weight) (BW). Do not inject more than 10 mL per injection site. Do not puncture the opposite viable size more than the tested number of punctures, shown in Table 1.

Clinical field studies indicate that administration of Zuprevo 18% (tildipirosin) Injectable Solution is effective for the control of respiratory disease in beef and non-lactating dairy cattle at “high risk” of developing BRD. Caves at high risk of developing BRD typically experience one or more of the following risk factors:

- Difficulties with multiple sows/litter
- Extended transport times and shrink
- Exposure to wet or cold weather conditions or wide temperature swings
- Exposure to weather conditions or wide temperature swings
- Animal nutrition problems (such as constipation, dehydration, or branding)
- Recent weaning and poor vaccination history

WARNINGS: 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.

Avoid direct contact with skin and eyes. If accidental eye exposure occurs, rinse eyes with clean water. If accidental skin exposure occurs, wash the skin immediately with soap and water. Tildipirosin may cause sensitization by skin contact.

For technical assistance or to report a suspected adverse reaction, call: 1-800-219-9286.

For customer service or to request a Material Safety Data Sheet (MSDS), call: 1-800-211-3573.

For additional Zuprevo 18% information go to www.zuprevo.com.

For a complete listing of adverse reactions for Zuprevo 18% reported to CVM see:

http://www.fda.gov/AnimalVetinary/SafetyHealth/

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.

RESIDUE WARNING: Cattle intended for human consumption must not be slaughtered within 21 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. Use of the 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.

PRECAUTIONS: 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 the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

CLINICAL PHARMACOLOGY: Similar to other macrolides, tildipirosin inhibits essential bacterial protein biosynthesis with selective binding to ribosomal subunits in a bacteriostatic and time-dependent manner. Tildipirosin may be associated with a fatty residue in swine. Tildipirosin concentrations in bronchial fluid collected in vivo from non-anesthetized cattle reflect the bacterial exposure to drug concentrations at the site of action.


MICROBIOLOGY: Tildipirosin has shown in vitro and in vivo antibacterial activity against the bacteria M. haemolytica, P. multocida, and H. somni; three pathogens associated with BRD.

The minimum inhibitory concentrations (MICs) of tildipirosin against the indicated BRD bacteria were determined using the methods described in the M31-A2 standard of the Clinical and Laboratory Standards Institute (CLSI) and are shown in Table 4.

The MICs of tildipirosin were determined for isolates of M. haemolytica, P. multocida, and H. somni obtained from two field studies. In both studies, tested isolates of M. haemolytica and P. multocida were obtained from nasopharyngeal swabs taken prior to treatment from all study animals. Tested isolates of H. somni were obtained from nasopharyngeal swabs taken prior to treatment from all study animals and from nasopharyngeal swabs taken from salineterminated animals classified as treatment failures.

Field studies in the U.S.

Time (hours) | Bronchial fluid (BF) concentration (ng/mL) | Plasma (P) concentration (ng/mL) | BF/P Ratio
--- | --- | --- | ---
4 | 1545 | 895 | 1.75
10 | 2975 | 1279 | 2.34
24 | 3448 | 1433 | 2.41
72 | 3489 | 1712 | 2.05
96 | 1644 | 2024 | 0.81
120 | 1619 | 1629 | 0.99
240 | 1937 | 1416 | 1.36
332 | 1225 | 1682 | 0.74
504 | 935 | 1032 | 0.89

Tildipirosin concentrations in bronchial fluid collected in vivo from non-anesthetized cattle reflect the bacterial exposure to drug concentrations at the site of action.

The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

The correlation between in vitro susceptibility data and clinical effectiveness is unknown.

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EFFECTIVENESS: In a multi-location field study, calves with naturally occurring BRD were treated with tildipirosin. The treatment success rate of the tildipirosin-treated group was compared to the treatment success rate in the saline-treated control group. A treatment success was defined as a call not designated as a treatment failure from Day 1 to 35 and with normal appetite, normal respiration, and a rectal temperature of -10°F on Day 14. The treatment success rate was significantly higher (p<0.003) for the tildipirosin-treated group (229/300, 76%) compared to the saline-treated control group (94/200, 47%). There were no BRD-related deaths in the tildipirosin-treated group compared to a 7% (21/300) BRD-related mortality rate in the saline-treated group.

In another multi-location field study, calves at high risk for developing BRD were administered tildipirosin. The treatment success rate of the tildipirosin-treated group was compared to the treatment success rate in the saline-treated control group. A treatment success was defined as a call not designated as a treatment failure based on clinical respiratory and appetite scoring and, if necessary, rectal temperature measurement of <104°F through the end of the study (Day 14). The treatment success rate was significantly higher (p<0.0001) for the tildipirosin-treated group (305/386, 79%) compared to the saline-treated group (197/387, 51%). There were no BRD-related deaths during the study (one tildipirosin-treated calf and two saline treated calves).

Similar to other macrolides, tildipirosin inhibits essential bacterial protein biosynthesis with selective binding to ribosomal subunits in a bacteriostatic and time-dependent manner. Tildipirosin may be associated with a fatty residue in swine. Tildipirosin concentrations in bronchial fluid collected in vivo from non-anesthetized cattle reflect the bacterial exposure to drug concentrations at the site of action.

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The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.