Introduction
The objective of this project was to evaluate the long-term efficacy of two antimicrobials (Zuprevo and Draxxin) on mitigation of pulmonary lesions in calves challenged with *M. haemolytica* 10 days post-treatment. All study procedures were conducted in accordance with a protocol (#3198) approved by the Kansas State University Institutional Animal Care and Use Committee.

Key Points
- This Technical Service Bulletin is derived from the first peer-reviewed, published article showing greater reduction in lung lesions by Zuprevo than Draxxin.
- In total, these findings illustrate that following a *M. haemolytica* challenge 10 days post-administration of saline (SAL), Draxxin (DRX), or Zuprevo (ZUP), the ZUP calves had less severe pneumonia than the SAL or DRX calves.
- ZUP demonstrated bactericidal activity and statistically significant superiority of DRX and SAL in clinical illness scores and pulmonary lesions.

Materials and Methods
Test animals were 38 local auction barn-derived calves, with an average weight of 391 lb. The day of arrival at the feeding facility (Day 0), five calves were reserved as replacements for any calves that became ill prior to initiation of the study. The remaining 33 calves were randomly assigned to one of three replicates, and treatments were administered.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Calves</th>
<th>Treatment</th>
<th>Dose per kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>12 head</td>
<td>Zuprevo (ZUP)</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Group 2</td>
<td>12 head</td>
<td>Draxxin (DRX)</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Group 3</td>
<td>9 head</td>
<td>Saline (SAL)</td>
<td>0.02 mL</td>
</tr>
</tbody>
</table>

10 days post-treatment, calves were administered an endoscopically guided *M. haemolytica* challenge to the first bronchus accessory lobe.

Three days post-challenge, calves were harvested. Primary outcomes of interest were percent lung lesions, lung-to-body weight ratios, and clinical illness scores (CIS).

Project Timeline
- **Treatment**: Day 0
- **Challenge**: 10 days post-treatment
- **Harvest**: 3 days post-challenge

**TECHNICAL BULLETIN**

Determination of the amount of pulmonary lesions when cattle are challenged with *Mannheimia haemolytica* 10 days after administration of either tildipirosin (Zuprevo™) or tulathromycin (Draxxin®)\(^1,2\)

**IMPORTANT SAFETY INFORMATION: FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE.**

**ZUPREVO™ You’re in control**

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2. Derek Mosier; Department of Diagnostic Medicine and Pathobiology, Kansas State University, 1600 Denison Ave. Manhattan, Kansas 66502.
Results

For the reader’s convenience and ease of understanding, results will be presented primarily in graph format, with an appendix of lung pathology photos for further clarification of product efficacy. First a summary of significant P values that may not be further addressed in the text:

- **Clinical Signs Post-Challenge**: ZUP<DRX & SAL P<0.05
- **Respiratory Rate Scores Post-Challenge**: ZUP & DRX<SAL P<0.05
- **Lung Lesions**: overall percentages of lung consolidation, ZUP<DRX & SAL P<0.05
- **Lung Percent of Body Weight**: ZUP<DRX & SAL P<0.05

### Figure 1: Clinical Signs Post-Challenge

![Clinical Signs Post-Challenge Graph](image1)

- Probability of showing clinical signs post challenge:
  - ZUP<DRX & SAL (P<0.05)

- **Percent of calves with abnormal CIS (CIS>0)**

- **Study day (day 10 = challenge administration)**

- **ZUP (n = 12)**
- **DRX (n = 12)**
- **SAL (n = 9)**

### Figure 2: Respiratory Rate Scores Post-Challenge

![Respiratory Rate Scores Post-Challenge Graph](image2)

- **ZUP<DRX (P = 0.12)**
- **ZUP & DRX<SAL (P = 0.05)**

- **Percent of calves with abnormal respiratory scores**

- **Study day (day 10 = challenge administration)**

- **ZUP (n = 12)**
- **DRX (n = 12)**
- **SAL (n = 9)**
Average collective scores per treatment group:

ZUP = 8.7  DRX = 13.1
SAL = 25.5  ZUP<DRX & SAL (P<0.05)

Treatment results: Bacteriology

A major difference was observed between Zuprevo and Draxxin, with *M. haemolytica* recovered in 100% (12/12) of calves’ lungs from Draxxin-treated calves, the same as in saline control calves. *M. haemolytica* was recovered from 25% (3/12) of Zuprevo-treated calves.

Discussion and Conclusion

Since the percentage of pulmonary lesion is an estimated value, another more precise quantitative measurement to determine the amount of pulmonary damage is the total lung weight as a percent of the animal’s body weight. In this study, the pulmonary percent of body weight agreed with the overall level of lung lesions for calves in the SAL and DRX groups, with both groups having higher lung percent of body weight compared to ZUP calves.

The probability of calves in the DRX group receiving abnormal clinical scores was higher than ZUP-treated calves in the CIS and appetite. Calves in the SAL-treated group had the highest probabilities of all groups for receiving abnormal scores. These clinical observations agree with the necropsy findings related to the level of pulmonary lesions in each group.

In total, these findings illustrate that following an *M. haemolytica* challenge 10 days post-administration of SAL, DRX, or ZUP, the ZUP calves had less severe pneumonia than the SAL or DRX calves; ZUP demonstrated bactericidal activity and statistically significant superiority over Draxxin and saline in clinical illness scores and pulmonary lesions; and this Technical Service Bulletin is derived from the first peer-reviewed, published article showing greater reduction in lung lesions by Zuprevo than Draxxin.³
Appendix, Lung Pathology Photos

Slide identity is—left to right—calf number, treatment product abbreviation, lung lesion score using all lung lobes; and lung lesion score using cranio-ventral lobes only.

<table>
<thead>
<tr>
<th>Saline Treated Calves</th>
<th>Draxxin Treated Calves</th>
<th>Zuprevo Treated Calves</th>
</tr>
</thead>
<tbody>
<tr>
<td>#37, SAL, 12.82%, 35.06%</td>
<td>#30, DRX, 27.8%, 48.8%</td>
<td>#9, ZUP, 3.6%, 9.4%</td>
</tr>
<tr>
<td># 35, SAL, 39.80%, 76.92%</td>
<td>#10, DRX, 6.3%, 18.2%</td>
<td>#7, ZUP, 39.1%, 77.8%</td>
</tr>
<tr>
<td>#16, SAL, 34.43%, 74.42%</td>
<td>#18, DRX, 26.4%, 68.6%</td>
<td>#13, ZUP, 3.3%, 9.5%</td>
</tr>
<tr>
<td></td>
<td>#30, DRX, 27.8%, 48.8%</td>
<td></td>
</tr>
</tbody>
</table>
(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 to citric acid monohydrate added to adjust pH.

**CHEMICAL NOMENCLATURE AND STRUCTURE:** Tildipirosin is the nonproprietary name for (11E,13E)-14R,55,65,7R,9R,15R,16R-6-[[4-Dimethylamino]3,5-dihydroxy-6-methyltetrahydro-2-pyran-2-yl]oxy]-16-ethyl-4-hydroxy-5,9,13-trimethyl-7-[[2-piperidin-1-yl]ethoxy]-1-piperidin-1-yl]piperazine-11,13-dione, 1:1. The empirical formula is C₃₁H₅₅NO₂₅. 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 side of the neck 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. Cattle at high risk of developing BRD typically experience one or more of the following risk factors:

-**Emaciation** from multiple safe barns/sources
-**Extended transport times and shrink**
-**Commingling from multiple sale barns/sources**
-**Stressful arrival processing procedures** (such as castration, dehorning, or branding)
-**Number of punctures tested in the in-use study**

**WARNINGS:** FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN TO AVOID ACCIDENTAL INJECTION. DO NOT USE IN AUTOMATICAPOWERED 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 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: WSAV.

**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 this product in these cattle may cause milk residues. A withdrawal period has not been established in prepubertal 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 swelling 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 bactericidal against certain isolates of M. haemolytica and P. multocida.

The following plasmid pharmacokinetic (PK) properties of tildipirosin have been observed following a subcutaneous injection of a dose of 4 mg/kg BW in the neck:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>775</td>
<td>284</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**AUCmax Area under the plasma concentration versus time curve measured from time zero to the last sample with tildipirosin concentrations exceeding the limit of quantification of the analytical method**

**INDICATED PATHOGENS:** Zuprevo 18% has shown in vitro and in vivo antibacterial activity against the bacteria M. haemolytica, P. multocida, and H. somni; three pathogens associated with BRD.

**MICS:** The minimum inhibitory concentrations (MICs) of tildipirosin against the indicated BRD pathogens were determined using the methods described in the M31-A2 standard of the Clinical and Laboratory Standards Institute (CLS) and are shown in Table 2.

**MICs** of tildipirosin were determined for isolates of M. haemolytica, P. multocida, and H. somni obtained from two BRD 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 saline-treated animals classified as treatment failures.

**ANIMAL SAFETY:** A target animal safety study was conducted using Zuprevo 18% administered in 5-month-old cattle as three subcutaneous doses of 4, 12, or 20 mg/kg BW given 7 days apart (3X, 9X, and 15X the labeled dose).

**STORAGE CONDITIONS:** Do not store above 30°C (86°F). Do not freeze. The maximum storage time after first punching is 28 days at or below 25°C (77°F).

**HISTORY:** Zuprevo 18% is supplied in 50, 100, and 250 mL amber glass, sterile, multi-dose vials. U. S. Patent: 6,514,946

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