Histophilosis: The compelling case for using Zuprevo™ in treatment of BRD caused by *Histophilus somni*

Histophilosis or *Histophilus somni*-associated disease is a common disease complex of North American cattle. *H. somni* causes an acute, often fatal, septicemic disease that can involve the respiratory, cardiovascular, musculoskeletal or nervous systems either singly or together in a confined group of cattle. In cattle on pasture, occasional reproductive events are reported, particularly late-term abortions. Recently weaned calves are at higher risk of infection and death from histophilosis than previously weaned older calves, yearlings, or mature animals. The risk of infection with *H. somni* is highest early in the feeding period with “high-risk” calves in confinement establishing peak *H. somni* titers at about 21 to 23 days after arrival. The clinical disease is often seen earlier in the feeding period, but the average death is often 30 to 60 days on feed.¹

*H. somni* is a gram-negative, non-motile, pleomorphic organism that prefers enriched broth under microaerophilic conditions for ideal growth. This makes it difficult to obtain isolates from typically collected nasal or deep pharyngeal swabs taken in the field and shipped to the lab. Samples need to be transported in special anaerobic media. Recent laboratory advances allow the use of PCR on nasal swabs and tissue samples. *H. somni* is considered a commensal organism of bovine mucous membranes, with both pathogenic and non-pathogenic strains being frequently found in the prepuce of bulls, the vagina of both cows and heifers and in the nasal passages². The organism produces both an exotoxin and endotoxins. In an active pathogenic state, it avoids being killed by phagocytic cells, thus avoiding an animal’s immune response by residing as an intracellular organism in host cells. This characteristic also makes it more difficult to be reached by most antibiotics.

**Key Features of Zuprevo 18% (tildipirosin)³**

- Zuprevo exhibits *in vitro* bacteriostatic and bactericidal action in bovine respiratory pathogens.
- Against *P. multocida* and *H. somni*, Zuprevo tends to be bacteriostatic, as the Minimal Bactericidal Concentration (MBC) generally is higher than the Minimum Inhibitory Concentration (MIC).
- Against *M. haemolytica*, Zuprevo is bactericidal, as the majority of isolates tested showed no difference in MIC versus MBC.
- The *in vitro* activity of tildipirosin is pH-dependent, showing highest activity at basic pH levels that are often found in diseased lung tissue.
- Tildipirosin produces a post-antibiotic effect (PAE) that varies between less than one hour and multiple hours depending on the bacterial species. The PAE is generally longer in the slow-growing, fastidious pathogen *H. somni* in comparison to both *M. haemolytica* and *P. multocida*.
- Against *H. somni*, Zuprevo has an MIC₉₀ of 4 ug/mL for both control and treatment of the organism.
- Zuprevo is passed into nasal secretions for at least 8 days after administration.

**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 cattle 20 months of age or older. A withdrawal period has not been established in pre-ruminating 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.**
Point 1: Zuprevo in lung tissue
Of all the antibiotics on the market in the United States, Zuprevo provides the highest level of drug in lung tissue for the longest period of time. Tissue levels above 5.0 µg/mL are found at 14 days after injection. This level is 20% above the 4 µg/ml MIC\textsubscript{90} for \textit{H. somni}. Zuprevo given at the label dose of 4 mg/kg BW (1 mL/CWT), has therapeutic levels of the drug in lung tissue 2.25 times higher than the \textit{H. somni} MIC\textsubscript{90} at 4 hours and 3.7 times at 24 hours after administration. By contrast, Draxxin\textsuperscript{®} reaches its MIC\textsubscript{90} by 24 hours post-administration at label dose and falls below therapeutic levels shortly thereafter. In pneumonic lung, Draxxin fails to reach MIC\textsubscript{90} values at any time post-administration\textsuperscript{4}.

Point 2: Zuprevo Chemical Properties
Zuprevo is a 16-membered ring, tri-basic macrolide that inhibits protein synthesis of the bacterial ribosome. It is easily absorbed into tissue and bacterial cell walls but due to its large size is difficult to excrete from cells. \textit{H. somni} is a fastidious, slow growing organism that is an ideal candidate for a drug like Zuprevo due to its ability to reach high tissue concentrations and long tissue activity level.

Point 3: Is \textit{H. somni} a problem in today’s cattle populations?
\textit{H. somni} is frequently isolated in lung, heart, brain and joint tissue from clinical cases. In a recent Kansas State Veterinary Diagnostic Laboratory report, over a three-year period \textit{H. somni} was isolated from 16% to 27% of pneumonic lung samples submitted, with from 39% to 56% of those isolates found to have multi-drug resistance to three or more commonly used antibiotics. In the Lubbers report, nasopharyngeal swabs from cattle at arrival prior to antibiotic treatment found an average of 6.1% of over 440 swabs culture-positive for \textit{H. somni}\textsuperscript{5}. Similar results have been reported from diagnostic labs in Nebraska, Oklahoma and Iowa\textsuperscript{6,7,8}.

Point 4: Can Zuprevo control \textit{H. somni} populations when used at arrival?
In a 2011 study of cattle purchased in Tennessee and transported to Nebraska for feeding, valuable information was obtained on the population dynamics of \textit{H. somni} in high-risk cattle! Cattle either received Zuprevo at arrival or a placebo. The study lasted for 42 days. Zuprevo significantly reduced sickness and improved performance over controls, specifically for \textit{H. somni}. In the control group \textit{H. somni} from nasal swabs continued to increase over the entire observational period (Figure 1), whereas in cattle receiving Zuprevo, \textit{H. somni} levels remained significantly lower. This demonstrates that while \textit{H. somni} increases in a population of animals over time, Zuprevo provides excellent control in holding down bacterial growth. This was also evident at necropsy, as none of the Zuprevo treated cattle had \textit{H. somni} isolated from lung tissue.
**SUMMARY**

Zuprevo is an antibiotic for rapid and sustained control or treatment of respiratory pathogens, particularly *H. somni*. Its established MIC<sub>90</sub> is well within lung tissue ranges for *M. haemolytica*, *P. multocida* and *H. somni*. For the respiratory pathogens *P. multocida* and *H. somni*, *in vitro* testing of tildipirosin indicates a tendency for bacteriostatic action. *In vitro* activity of tildipirosin is pH-dependent, showing highest activity at basic pH levels, which are pH levels frequently found in diseased bovine lung tissue, making it an excellent choice as a treatment product. Zuprevo is above the MIC<sub>90</sub> in lung tissue for over 14 days, which is superior to the therapeutic characteristics of Draxxin for *H. somni*.

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### References

4. Pfizer FOI for Draxxin (tulathromycin) NADA 141-244.
6. UNL Diagnostic Center News Spring 2013, Doster and Seelmeyer.
8. ISU DX Lab Summary, data on file
**Zuprevo**

**18%**

**(Tildipirosin)**

**Injectable Solution for Cattle**

**ANTIMICROBIAL DOSE:**

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 semi-synthetic macrocyclic antibiotic. Each mL of Zuprevo contains 180 mg of tildipirosin as the free base, 82.5 mg citric acid monohydrate and 400 mg propylene glycol, and water with as citric acid monohydrate added to adjust pH.

**CHEMICAL NOMENCLATURE AND STRUCTURE:**


**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*.

**DOSEAGE 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 stopper of the respective vial 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:

- Contaminating from multiple site barns/sources
- Extended transport times and shear
- Exposure to cold or wet weather conditions or wide temperature swings
- Stressful arrival processing procedures (such as castration, dehorning, or branding)
- Recent wearing and poor vaccination history

**WARNING:** Use Only as Directed

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

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

**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 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.

**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 proteinbiosynthesis with selective binding to bacterial 23S rRNA in a bacteriostatic and time-dependent manner. Tildipirosin may be bacteriostatic against certain isolates of *M. haemolytica* and *P. multocida*.

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

**Table 2 Summary of pharmacokinetic characteristic of tildipirosin administered subcutaneously to calves at a dose of 4 mg/kg BW.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀ (ng/mL)</td>
<td>767</td>
<td>284</td>
</tr>
<tr>
<td>C₅₀ (hr)</td>
<td>0.75</td>
<td>0.43</td>
</tr>
<tr>
<td>AUC₀→t (hr·ng/mL)</td>
<td>2107</td>
<td>3499</td>
</tr>
<tr>
<td>AUC₅₀→t (hr·ng/mL)</td>
<td>2493</td>
<td>5908</td>
</tr>
<tr>
<td>T₅₀ (hr)</td>
<td>210</td>
<td>53</td>
</tr>
</tbody>
</table>

* Values based on 10 animals

**Table 3 Bronchial-fluid to plasma ratio of tildipirosin in non-anesthetized cattle following a subcutaneous injection at a dose of 4 mg/kg BW in the neck.**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Bronchial fluid (BF) concentration (ng/g)</th>
<th>Plasma (P) concentration (ng/mL)</th>
<th>BF/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1543</td>
<td>895</td>
<td>1.75</td>
</tr>
<tr>
<td>10</td>
<td>2975</td>
<td>1279</td>
<td>2.36</td>
</tr>
<tr>
<td>24</td>
<td>3448</td>
<td>1432</td>
<td>2.42</td>
</tr>
<tr>
<td>72</td>
<td>3849</td>
<td>1712</td>
<td>2.25</td>
</tr>
<tr>
<td>96</td>
<td>1644</td>
<td>2024</td>
<td>0.82</td>
</tr>
<tr>
<td>120</td>
<td>1619</td>
<td>1629</td>
<td>0.99</td>
</tr>
<tr>
<td>240</td>
<td>1937</td>
<td>1416</td>
<td>1.38</td>
</tr>
<tr>
<td>336</td>
<td>1225</td>
<td>1682</td>
<td>0.74</td>
</tr>
<tr>
<td>360</td>
<td>935</td>
<td>1032</td>
<td>0.90</td>
</tr>
</tbody>
</table>

**Table 4 Tildipirosin minimum inhibitory concentration (MIC) values of indicated pathogens isolated from BRD field studies in the U.S.**

<table>
<thead>
<tr>
<th>Indicated Pathogens</th>
<th>Year of isolation</th>
<th>Study</th>
<th>Number of isolates</th>
<th>MIC₅₀** (μg/mL)</th>
<th>MIC₉₀** (μg/mL)</th>
<th>MIC range</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mannheimia haemolytica</em></td>
<td>2007</td>
<td>Treatment</td>
<td>484</td>
<td>2</td>
<td>2</td>
<td>0.25 to 32</td>
</tr>
<tr>
<td></td>
<td>2007 to 2008</td>
<td>Control</td>
<td>178</td>
<td>1</td>
<td>1</td>
<td>0.25 to 32</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em></td>
<td>2007</td>
<td>Treatment</td>
<td>255</td>
<td>0.5</td>
<td>1</td>
<td>0.12 to 32</td>
</tr>
<tr>
<td></td>
<td>2007 to 2008</td>
<td>Control</td>
<td>273</td>
<td>0.5</td>
<td>1</td>
<td>0.03 to 4</td>
</tr>
<tr>
<td><em>Histophilus somni</em></td>
<td>2007</td>
<td>Treatment</td>
<td>53</td>
<td>2</td>
<td>4</td>
<td>1 to 4</td>
</tr>
<tr>
<td></td>
<td>2007 to 2008</td>
<td>Control</td>
<td>32</td>
<td>2</td>
<td>4</td>
<td>1 to 4</td>
</tr>
</tbody>
</table>

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

**Table 3 Bronchial-fluid to plasma ratio of tildipirosin in non-anesthetized cattle following a subcutaneous injection at a dose of 4 mg/kg BW in the neck.**

Due to the extensive partitioning of macrolides into tissues and because of their multi-fold greater concentrations in bronchial fluid relative to that observed in the blood, plasma drug concentrations underestimate concentrations at the site of action.

**Table 4 Tildipirosin minimum inhibitory concentration (MIC) values of indicated pathogens isolated from BRD field studies in the U.S.**

**ANIMAL SAFETY:** A target animal safety study was conducted using Zuprevo 18% administered in 5-month-old calves as a single subcutaneous injection of 4, 12, or 20 mg/kg BW given 7 days apart (1X, 3X, and 5X the labeled dose). Animals remained clinically healthy during the study at the labeled dose. Injection site swelling and inflammation, initially severe in some animals, was observed that persisted to the last day of observation (21 days after injection). No other drug-related lesions were observed macroscopically or microscopically at the labeled dose.

A separate injection site tolerance study was conducted using Zuprevo 18% in 5- to 9-month-old cattle administered as a single subcutaneous injection of 10 mL. Injection site swelling and inflammation, initially severe in some animals, was observed that persisted to the last day of observation (35 days after injection). No other drug-related clinical signs were observed.

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

**HOW SUPPLIED:** Zuprevo 18% is supplied in 50, 100 and 250 mL amber glass, sterile, multidose vials.

U. S. Patent: 6,514,946

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