Controlling Bovine Respiratory Disease (BRD) in Calves on Arrival

A comparison of ZACTRAN® (gamithromycin) and DRAXXIN® (tulathromycin)¹

¹ Data on file at Merial.

IMPORTANT SAFETY INFORMATION: For use in cattle only. Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in female dairy cattle 20 months of age or older, or in calves to be processed for veal. The effects of ZACTRAN on bovine reproductive performance, pregnancy and lactation have not been determined.
Both are in the macrolide class of antimicrobials.
Both have demonstrated clinical efficacy.
Both DRAVIN and ZACTRAN are macrolides; both are approved for treatment and control of BRD*.
They differ in chemical structure and formulation.

*ZACTRAN is indicated for the treatment of BRD associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis 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 and P. multocida.

Control Study Background1
- Calves sourced from southeast auction market (classified as high risk)
- Trucked to two commercial feedyards in two states (classified as long-haul)
- Enrollment October to December 2010: 17 replicates (34 pens) of cattle followed to closeout (2,529 total cattle)
- Study conducted according to CVM/FDA regulation following Good Clinical Practice (GCP) guidelines
- Calves randomized and enrolled into a ZACTRAN or DRAVIN study group during arrival processing (within 24 hours of arrival to feedyard)
- Placed in randomly selected ZACTRAN or DRAVIN pen (no commingling)
- Observed 1-2 times daily for BRD by blinded qualified feedyard personnel

Control Study Protocol1
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Control Study Results1
Both ZACTRAN and DRAVIN performed well and compared favorably for the control of bovine respiratory disease in highly stressed cattle.

<table>
<thead>
<tr>
<th></th>
<th>ZACTRAN</th>
<th>DRAVIN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial weights (lbs.)</td>
<td>503</td>
<td>503</td>
<td>0.97</td>
</tr>
<tr>
<td>Rectal temperature (°F) (at enrollment)</td>
<td>102.7</td>
<td>102.7</td>
<td>0.72</td>
</tr>
<tr>
<td>BRD morbidity rate (%) (first pull)</td>
<td>31.0</td>
<td>22.9</td>
<td>0.03*</td>
</tr>
<tr>
<td>Retreatments (%)</td>
<td>41.5</td>
<td>39.6</td>
<td>0.71</td>
</tr>
<tr>
<td>BRD mortality (%)</td>
<td>3.5</td>
<td>3.3</td>
<td>0.90</td>
</tr>
<tr>
<td>Case fatality rate (%)</td>
<td>14.8</td>
<td>19.5</td>
<td>0.31</td>
</tr>
<tr>
<td>Final weights (closeout weights) (lbs.)</td>
<td>1,165</td>
<td>1,164</td>
<td>0.90</td>
</tr>
<tr>
<td>Average daily gain (ADG) (lbs./day)</td>
<td>2.65</td>
<td>2.65</td>
<td>0.99</td>
</tr>
<tr>
<td>Feed to gain ratio (F:G)</td>
<td>6.04</td>
<td>6.06</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* No significant difference in morbidity was seen at the Nebraska site. However, a higher first-pull rate was found with ZACTRAN at the Kansas site (P<0.01).

IMPORTANT SAFETY INFORMATION: For use in cattle only. Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in female dairy cattle 20 months of age or older, or in calves to be processed for veal. The effects of ZACTRAN on bovine reproductive performance, pregnancy and lactation have not been determined.

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150 mg/mL ANTMICROBIAL

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.

READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT.

DESCRIPTION

ZACTRAN® Injection for Cattle is a ready to use sterile parenteral solution containing gamithromycin, a macrolide sub-class, 7a-azalide antimicrobial. Each mL of ZACTRAN contains 150 mg of gamithromycin as the free base, 1 mg of monohydrated glycol and 40 mg of sucrose acid in a glycerol formal liquid.

The chemical name of gamithromycin is 1-Oxa-7-azacyclopentadecan-15-one,13-(2,6-dideoxy-3-C-methyl-3-0-methyl-alpha-L-ribo-hexopyranosyl)oxy-2-ethyl-3,4,10-trihydroxy 5,8,10,12,14-hexamethyl-7-propyl-11-(1)-(3,4,6-trideoxy-3-C-methyl-dimethylamino)-beta-D-xylene-hexopyranosyl](C28H48O21N6)[(µg/mL)

<table>
<thead>
<tr>
<th>Indicated Pathogens</th>
<th>Years of isolation</th>
<th>NS of isolation</th>
<th>MIC** (µg/mL)</th>
<th>MIC range (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. somni</td>
<td>2004</td>
<td>89</td>
<td>1</td>
<td>0.5 to &gt;32</td>
</tr>
<tr>
<td>M. haemolytica</td>
<td>2004</td>
<td>79</td>
<td>0.5</td>
<td>0.12 to &gt;32</td>
</tr>
<tr>
<td>P. multocida</td>
<td>2012</td>
<td>32</td>
<td>0.5</td>
<td>0.25 to 1</td>
</tr>
</tbody>
</table>

* 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

The effectiveness of ZACTRAN for the treatment of BRD associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni was demonstrated in a field study conducted at four geographic locations in the United States. A total of 497 cattle exhibiting clinical signs of BRD were enrolled in the study. Cattle were administered ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline as a subcutaneous injection once on Day 0. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10. The percentage of successes in cattle treated with ZACTRAN (58%) was statistically significantly higher (p<0.05) than the percentage of successes in the cattle treated with saline (19%).

RESIDUE WARNINGS

Do not treat cattle within 35 days of slaughter. Because a discard time in milk has not been established, do not use in dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-nuclaming calves. Do not use in calves to be processed for veal.

PRECAUTIONS

The effects of ZACTRAN on bovine reproductive performance, pregnancy, and lactations have not been determined. Subcutaneous injection of ZACTRAN may cause a transient local tissue reaction in some cattle that may result in trim loss of edible tissues at slaughter.

ADVERSE REACTIONS

Transient animal discomfort and mild to moderate injection site swelling may be seen in cattle treated with ZACTRAN.

CLINICAL PHARMACOLOGY

The macrolide antimicrobials as a class are weak bases and as such concentrate in some tissues (such as pulmonary leukocytes). Prolonged exposure of extracellular pulmonary pathogens to macrolides appears to reflect the slow release of drug from its intracellular reservoir to the site of action, the pulmonary epithelial lining fluid (ELF). It is the ELF that is relevant to the successful treatment and control of BRD. Gamithromycin is primarily bacteriostatic at therapeutic concentrations. However, in vitro bacterial activity has been observed at concentrations of 10 µg/mL (Mueller-Hinton broth) and after exposure to the 6-hour and 24-hour plasma samples derived from cattle dosed at 6 mg gamithromycin/kg BW. Macrolides typically exhibit substantially higher concentrations in the alveolar macrophages and ELF as compared to concentrations observed in plasma. Gamithromycin concentrations in the ELF and ELF cells exceed the concentrations observed in the plasma. Postmortem gamithromycin concentrations in ELF exceed the MIC of M. haemolytica, H. somni, and P. multocida through at least 72 hours after drug administration. Because M. haemolytica, P. multocida and H. somni are extracellular pathogens, drug concentrations in the ELF are considered to be clinically relevant. The postmortem area under the concentration-time curve (AUC) observed in lysed ELF cells (e.g., alveolar macrophages) are at least 300-times greater than that in the plasma. Although published studies suggest that inflammation can increase the release of drug from macrophages and neutrophils, these high concentrations in the alveolar macrophages should not be considered indicative of the magnitude or duration of response to the pathogens for which this product is indicated.

ZACTRAN administered subcutaneously in the neck of cattle at a single dosage of 6 mg/kg BW is rapidly and completely absorbed, with peak concentrations generally occurring within 1 hour after administration. Based upon plasma and lung homogenate data, the terminal half-life (T½) of gamithromycin is approximately 3 days. In vitro plasma protein binding studies show that 26% of the gamithromycin binds to plasma protein, resulting in free-drug available for rapid and extensive distribution into body tissues. The free drug is rapidly cleared from the systemic circulation with a clearance rate of 712 mL/hr/kg and a volume of distribution of 25 L/kg. Dose proportionality was established based on AUC over a range of 1 mg/kg BW to 9 mg/kg BW. Biliary excretion of the unchanged drug is the major route of elimination.

MICROBIOLOGY

The minimum inhibitory concentrations (MICs) of gamithromycin were determined for BRD isolates obtained from calves enrolled in BRD treatment field studies in the U.S. in 2004 using methods recommended by the Clinical and Laboratory Standards Institute (M31-A2). Isolates were obtained from pre-treatment nasopharyngeal swabs from each enrolled calf and from calves removed from the study due to BRD. The results are shown below in Table 1.

CONTRAINdications

As with all drugs, the use of ZACTRAN is contraindicated in animals previously found to be hypersensitive to this drug.

WARNING:

FOR USE IN CATTLE ONLY. NOT FOR USE IN HUMANS.

KEEP THIS AND ALL OTHER DRUGS OUT OF REACH OF CHILDREN. NOT FOR USE IN CHICKENS OR TURKEYS.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse effects, obtain an MSDS or for assistance, contact Merical at 1-888-637-4231.