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CAUTION: Federal law limits this drug to use under the professional supervision of a licensed veterinarian. Animal feed containing or containing this veterinary feed drug directive shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian’s professional practice.

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Implications
Feeding Pulmotil® reduces morbidity associated with Bovine Respiratory Disease (BRD).

Introduction – Impact of BRD
BRD is the most common disease among feedlot cattle, accounting for approximately 75% of feedlot morbidity and 50% to 70% of feedlot deaths.1-3,8 Costing the industry an estimated $800 to $900 million annually in economic losses due to reduced feed efficiency, treatment costs and death.4

Although mortality is of primary concern, morbidity (sickness) of cattle may cost even more than mortality considering the expenses associated with medication, additional labor requirements involved with treatment, premature culling because of chronic conditions, and the expense of reduced performance during and after an illness.5 The difference in average daily gain (ADG) between calves that remain healthy and calves that suffer from respiratory disease can be substantial. During 28-day receiving periods, Smith5 and Bateman6 et al. reported that ADG was 0.5 lbs less and 0.3 lbs less, respectively, in calves that became sick versus control calves.

The impact of subclinical BRD should also be considered. Approximately 65% to 80% of total morbidity within a feeding period occurs during the first 45 days.5 In a study identifying pulmonary lesions evident at slaughter, 35% of steers had received treatment for respiratory tract disease between birth and slaughter, whereas 72% had pulmonary lesions evident at slaughter. Among steers treated for clinical respiratory-tract disease, 78% had pulmonary lesions; 68% of untreated steers had pulmonary lesions. Pulmonary lesions at slaughter were associated (P < 0.01) with a 0.17-lb reduction in daily gain during the feeding period.7

Given the challenges of managing BRD, Elanco is committed to providing ongoing knowledge- and science-based solutions to help veterinarians more effectively manage the disease, including the subclinical impacts on animal health and resulting economic and performance losses.

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Pulmotil is the trademark for the feed formulation of the antibiotic tilmicosin. It is the first feed medication available to the beef industry requiring a licensed veterinarian to issue a valid Veterinary Feed Directive (VFD). Pulmotil was originally approved for use in swine in 1996 for the control of swine respiratory disease and was the first VFD medicated feed ingredient available to the livestock industry.

Study Objectives
The objectives of the four studies summarized in this report were:
• To collect data for the Food and Drug Administration (FDA) registration and approval of Pulmotil in cattle
• To demonstrate efficacy of Pulmotil for control of BRD associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni in groups of cattle in the early stages of a BND outbreak

Study Overview and Design
Four studies were conducted at various locations across North America during the fall and winter of two consecutive years (2007 and 2008). Steers and/or heifers were obtained from multiple auction markets or ranch sources, with no attempt to minimize variation within or across trials. The cattle represented a wide range of genotypes and phenotypes. A summary of each study is presented in Table 1.
The study design was a masked, negative-controlled, parallel-arm clinical efficacy study using a randomized complete block design. A standardized protocol was used across all studies. At each site, calves were individually weighed, ear tagged, physically examined to determine study eligibility and processed. Processing included a Ralgro® implant, administration of a four-way modified live viral vaccine (IBR, BVD, BRSV and PI-3), a seven-way clostridial vaccine and treatment for internal and external parasites with an avermectin. The use of vaccines against Pasteurella sp., Mannheimia sp., and/or Histophilus sp. was prohibited, as was metaphylactic antibiotic administration.

### Cattle management
Within 24 hours of arrival, calves were individually weighed, ear tagged, physically examined to determine study eligibility and processed. Processing included a Ralgro® implant, administration of a four-way modified live viral vaccine (IBR, BVD, BRSV and PI-3), a seven-way clostridial vaccine and treatment for internal and external parasites with an avermectin. The use of vaccines against Pasteurella sp., Mannheimia sp., and/or Histophilus sp. was prohibited, as was metaphylactic antibiotic administration.

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### Respiratory Scoring Criteria
- **Normal**: Normal respiratory rate and no symptoms
- **Mild**: Serous nasal or ocular discharge and/or cough
- **Moderate**: Mucous or mucopurulent nasal or ocular discharge and/or increased respiratory rate
- **Severe**: Recumbent, reluctant to stand, nonresponsive, ataxic, excess salivation delayed responsiveness

### Depression Scoring Criteria
- **Normal**: Bright, alert and responsive
- **Mild**: Isolated with head down, ears drooping, responsive
- **Moderate**: Isolated, head down, muscle weakness, delayed responsiveness
- **Severe**: Recumbent, reluctant to stand, nonresponsive, ataxic, excess salivation delayed responsiveness

### Efficacy Assessment
Throughout the course of each 28-day study, every calf was evaluated daily for signs of BRD. Animals identified as having severe signs of BRD (DS ≥ 3), regardless of rectal temperature, were classified as treatment failures and withdrawn from the study. Having been withdrawn from the study, these calves were treated with an injectable antibiotic.

On day 28, all remaining calves were evaluated for signs of BRD and classified as a treatment success or failure. A treatment success was defined as a calf with a DS of 0, an RS of 0 or 1, and a rectal temperature <104°F. Calves not meeting the success criteria were classified as treatment failures.

### Statistics
All health and performance variables were analyzed using a generalized linear mixed model (SAS Proc Glimmix) with treatment as the fixed effect and site, treatment by site, and block within site as random effects. Day 0 body weight was used as a covariate in the analysis of performance data.

### Results and Discussion
Pulmotil was fed for 14 days according to label instructions following the diagnosis of BRD in ≥ 10% of the study calves, and results were pooled across studies (Table 3). The number of calves classified as successes (healthy) at the end of the

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<thead>
<tr>
<th>Trial Number</th>
<th>Location</th>
<th>Season</th>
<th>Gender</th>
<th>Cattle Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>T5CC0728</td>
<td>Alberta</td>
<td>Nov/Dec</td>
<td>Steers</td>
<td>Alberta</td>
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<tr>
<td>T5C10729</td>
<td>Nebraska</td>
<td>Sept/Oct</td>
<td>Heifers</td>
<td>Iowa</td>
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<td>T5C060905</td>
<td>California</td>
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<td>Steers and Heifers</td>
<td>Idaho/Oregon</td>
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<tr>
<td>T5C160806</td>
<td>Idaho</td>
<td>Nov/Dec</td>
<td>Steers</td>
<td>Washington</td>
</tr>
</tbody>
</table>

### Table 2. BRD Depression and Respiratory Scoring Systems
<table>
<thead>
<tr>
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<tr>
<td>3 Severe</td>
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</tbody>
</table>

### Table 3. Effect of Feeding Pulmotil to Newly Received Calves: Four Registration Studies, 28-Day Summary
<table>
<thead>
<tr>
<th>Item</th>
<th>Control</th>
<th>Pulmotil</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial head</td>
<td>576</td>
<td>576</td>
<td>—</td>
</tr>
<tr>
<td>Initial weight, lbs*</td>
<td>538</td>
<td>537</td>
<td>—</td>
</tr>
<tr>
<td>Treatment success (healthy), %**</td>
<td>49.2</td>
<td>67.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Treatment failure (morbidity), %**</td>
<td>50.8</td>
<td>32.7</td>
<td>0.03</td>
</tr>
<tr>
<td>DMB*</td>
<td>10.9</td>
<td>11.0</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Arithmetic mean
**Least squares mean

No adverse effects were noted as a result of feeding Pulmotil.

### Table 3. Effect of Feeding Pulmotil to Newly Received Calves: Four Registration Studies, 28-Day Summary

No adverse effects were noted as a result of feeding Pulmotil.

### Study initiation
The studies began on the first day that ≥ 10% of all calves demonstrated BRD. All studies were initiated within five days of calf arrival at a respective site. The incidence of BRD outbreak ranged from 10.9% to 16.0% on the day of study initiation.

### Feeding and dosage
Pulmotil was fed during the first 14 days of the 28-day studies at a dosage of 0.0 or 12.5 mg tilmicosin/kg body weight/head/day. Pulmotil was mixed into the daily feed at between 631 and 664 g/ton (100 percent dry matter) to provide the appropriate dosage.

The cattle were fed, once per day, a standard receiving ration composed of ingredients typical of the geographic location of the respective trial site. A Type B medicated feed containing 18,140 g/ton tilmicosin was mixed into the ration at each site to arrive at the intended tilmicosin dosage level. An identical non-medicated Type B supplement was incorporated into the control ration.

### Graph 1. Accumulated Daily BRD-related Failures — All Sites

Graph 1 illustrates the cumulative BRD-related failures (morbidity) over the 28-day study. Feed intake was not different between control and Pulmotil treatments.
and pen was the experimental unit. The total number of calves of pens within site. The individual calf was the observational unit site, with 12 calves per pen. The blocking factor was the location at four study sites. There were six blocks of four pens at each clinical efficacy study using a randomized complete block design. The study design was a masked, negative-controlled, parallel-arm DS or RS of 3, regardless of temperature (Table 2). Calves with a respiratory score (RS) of 2 and a rectal temperature ≥ 104°F; or a depression score (DS) of 1 or 2 and a rectal temperature ≥ 104°F; or a ≥ for the 10% criteria was a calf demonstrating a depression negative control treatment. The definition of clinical illness used was metaphylactic antibiotic administration.

Study design
A standardized protocol was used across all studies. At each site, the cattle were commingled and observed daily for signs of BRD. Once the BRD outbreak was severe enough such that ≥ 10% of the calves were demonstrating clinical illness, the calves were randomly assigned to pens to begin receiving either Pulmotil or negative control treatment. The definition of clinical illness used for the ≥ 10% criteria was a calf demonstrating a depression score (DS) of 1 or 2 and a rectal temperature ≥ 104°F; or a respiratory score (RS) of 2 and a rectal temperature ≥ 104°F; or DS or RS of 3, regardless of temperature (Table 2). Calves with a DS or RS of 3 counted toward the 10% criteria, were treated with an injectable antibiotic, but were not returned to their pen nor included in the study. Tilmicosin medicated feed treatment has not been evaluated in cattle with severe clinical disease.

Cattle management

Within 24 hours of arrival, calves were individually weighed, ear tagged, physically examined to determine study eligibility and processed. Processing included a Ralgro® implant, administration of a four-way modified live viral vaccine (IBR, BVD, BRSV and Pi-3), a seven-way ophthalmic and treatment for internal and external parasites with an avermectin. The use of vaccines against Pasteurella spp., Mannheimia spp., and/or Histophilus sp. was prohibited, as was metaphylactic antibiotic administration.

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Efficacy Assessment
Throughout the course of each 28-day study, every calf was evaluated daily for signs of BRD. Animals identified as having severe signs of BRD (DS or RS = 3), regardless of rectal temperature, were classified as treatment failures and withdrawn from the study. Having been withdrawn from the study, these calves were treated with an injectable antibiotic.

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<td>Nov/Oct</td>
<td>Steers</td>
<td>Alberta</td>
</tr>
<tr>
<td>T5C310729</td>
<td>Nebraska</td>
<td>Sept/Oct</td>
<td>Hefers</td>
<td>Iowa</td>
</tr>
<tr>
<td>T5C060805</td>
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<td>Nov/Oct</td>
<td>Steers and Hefers</td>
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Results and Discussion
Pulmotil was fed for 14 days according to label instructions following the diagnosis of BRD in ≥ 10% of the study calves, and results were pooled across studies (Table 3). The number of calves classified as successes (healthy) at the end of the 28-day studies was greater in Pulmotil-fed calves, 67.3% vs. 49.2% (P = 0.03). Graph 1 illustrates the cumulative BRD-related failures (morbidity) over the 28-day study. Feed intake was not different between control and Pulmotil treatments.

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Graph 1. Accumulated Daily BRD-related Failures — All Sites

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<th>Item</th>
<th>Pulmotil Dosage, mg/kg BW/day</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>0.0</td>
<td>12.5</td>
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<td>Treatment failure (morbidity), %**</td>
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<tr>
<td>DMB=Dry matter basis</td>
<td>10.9</td>
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</table>

Graph 2. Cumulative Daily BRD-related Failures — By Study Number

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Summary of Four Registration Studies Assessing the Efficacy of Pulmotil® (tilmicosin) for the Control of Bovine Respiratory Disease in Cattle

Elanco Studies: T5CCA0728, T5C310729, T5C060805 and T5C160806

M. Corbin, DVM, PhD, K. Blue, DVM, and R. Williams, DVM, MBA

Elanco Animal Health

Implications

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