Field Efficacy Evaluation of Gamithromycin for Treatment of Bovine Respiratory Disease in Cattle at Feedlots

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ABSTRACT

Bovine respiratory disease (BRD) complex is the most common disease occurring in feedlot cattle. Vaccines and antibiotics remain the standard methods for prevention, control, and treatment. Gamithromycin is an azalide 15-membered semi-synthetic macrolide antibiotic that has been developed for treatment and prevention of BRD in feedlot cattle. Cattle, clinically ill with BRD, treated with gamithromycin at 6 mg/kg (2mL/50kg) by subcutaneous injection on Day 0, had significantly ($P<0.05$) lower mean depression scores, respiratory character scores, and rectal temperatures on daily assessments on Day 1 through the completion of the 10-day study than negative control cattle treated with saline. The percentage of overall treatment successes for cattle treated with gamithromycin was significantly ($P<0.05$) higher than in the control cattle treated with saline. Mortality also was significantly lower for cattle treated with gamithromycin (0.6%) than for control cattle treated with saline (8.5%). These results indicate that a single dose of gamithromycin at 6 mg/kg (2mL/50kg) is significantly effective as a treatment of for cattle showing clinical signs of BRD.

INTRODUCTION

Bovine respiratory disease (BRD) complex

is the most common disease occurring in feedlot cattle, and is a significant source of losses from poor performance and deaths. Calves become stressed by weaning, shipping, processing, commingling of different herds, weather, and overcrowding.[1-4] Stress compromises their immune system, leaving the animals susceptible to invasion by infectious agents. The most common viruses associated with BRD include bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), bovine respiratory synctial virus (BRSV), and parainfluenza type-3 virus (PI-3).[1,2,4] Exposure to these viruses can cause severe damage to the respiratory tract, and create opportunities for bacteria such as Mannheimia haemolytica and Pasteurella multocida, to colonize the lung. A study of feedlots in 12 states by the USDA-APHIS in 1999 reported that the incidence of clinical BRD was 14.4%.[5] Financial losses due to death, reduced feed efficiency, and treatment costs associated with BRD are estimated to run between $500 million and $900 million annually.[5,6]

Vaccines and antibiotics remain the standard methods for prevention, control, and treatment of BRD, but other methods, including genetic selection and various management practices, also have been evaluated.[1,4,7,8]

Gamithromycin is an azalide 15-membered semi-synthetic macrolide antibiotic that has been developed for treatment and prevention of BRD.[7,9,10] Studies of the pharmacokinetic and pharmacodynamic properties of gamithromycin showed that a single subcutaneous dose at 6 mg/kg provides rapid therapeutic and persistent activity in the control and prevention of infections. The studies described here were conducted in feedlots and research facilities in the United States to evaluate the efficacy of a single subcutaneous dose of gamithromycin at 6 mg/kg (2mL/50 kg) administered to cattle displaying signs of clinical illness for the treatment of BRD compared with effects of treating with sterile saline.

MATERIALS AND METHODS

Individual studies at four sites, identified as Site 1, Site 2, Site 3, and Site 4, comprising a single multi-centered randomized, negative control, blinded clinical field efficacy study, were conducted at different locations in the United States (Readstown, Wisconsin; Rockdale, Texas; Marshall, Missouri; and Fulton, Missouri, respectively) from September 22 to November 14, 2004. Animals in the study were managed similarly and with due regard for their well-being. Animals were handled in compliance with Merial Institutional Ani-

Table 1. Summary of animal descriptions by location

Site	Location	Number of animals enrolled	Number of animals treated	Number of animals in analysis	Breed	Approximate age (mo)	Weight range (kg)
1	Wisconsin	135 (77 F, 58 Mᵃ)	135	135	Cross	6-7	155-224
2	Texas	177 Mᵃ	177	176ᵇ	Cross	6-8	164-239
3	Missouri	132 F	131ᶜ	128ᵈ	Cross	6-10	130-262
4	Missouri	54 (21 F, 24 M, 9 MC)	54	53ᵉ	Pure or Cross	6-10	183-233

F=female; M=male, MC=male castrate
ᵃIntact and castrated males were not differentiated
ᵇExcludes one animal that was removed inadvertently
ᶜExcludes one animal that died from BRD prior to treatment, which was excluded according to the protocol
ᵈExcludes three animals removed for non-BRD conditions
ᵉExcludes one animal removed for non-BRD conditions

mal Care and Use Committee (IACUC) approvals and all applicable local regulations and requirements of any local IACUC. The study monitors ensured that these procedures were in compliance with the protocol.

Animals

Cattle were acquired from cattle suppliers, auction markets, and stockyards from multiple geographic locations. Of the cattle sourced a total of 498 crossbred and purebred beef cattle, including 230 heifers and 268 male or castrated male calves, 6 to 10 months of age and weighing 130 to 262 kg, were enrolled. The calves were trucked between 4 and 19.5 hours to the study sites (Table 1). Each animal had a uniquely numbered ear tag applied for identification purposes.

Inclusion Criteria

Only animals demonstrating clinical signs of BRD, which included all of the following criteria, were enrolled:

- A depression score ≥ 1
- Respiratory character score ≥ 1
- Rectal temperatures $\geq 40°C$ (104.0°F)

Exclusion Criteria

Cattle that were debilitated, suffering from systemic disease other than BRD, or were injured, fractious or otherwise unsuitable were excluded from enrollment. Animals known to have received bacterial vaccines for BRD, had been treated with antimicrobials within 30 days prior to enrollment, or had transit time to the study site in excess of 24 hours were excluded.

Allocation

At each location, all animals were from a single supplier of commingled calves from multiple origins. Day 0 (day of treatment) was the day of arrival and processing through two days after arrival. Day 0 was not the same for all cattle at each site; however, all cattle in a replicate were enrolled and treated on the same day. At all sites, animals within a replicate were allocated by a unique randomization schedule prepared by a biostatistician in a 2:1 ratio for cattle

Figure 1. *Summary of Average Depression Scores*
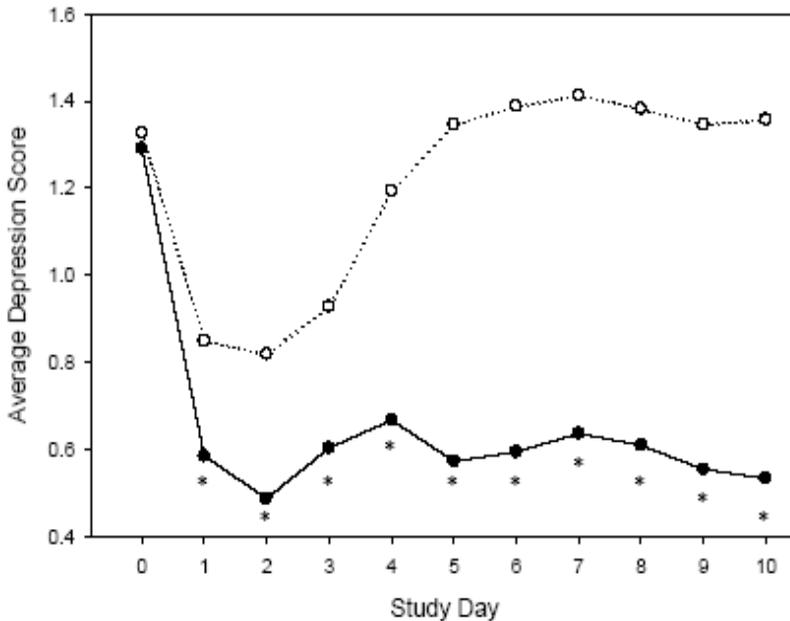
• *represent the average depression score for the Gamithromycin treated group*
o *represent the average depression score for the Saline injected group*
* *denotes a statistically significant difference (p < 0.05)*

Figure 2. *Summary of Average Respiratory Character Scores*
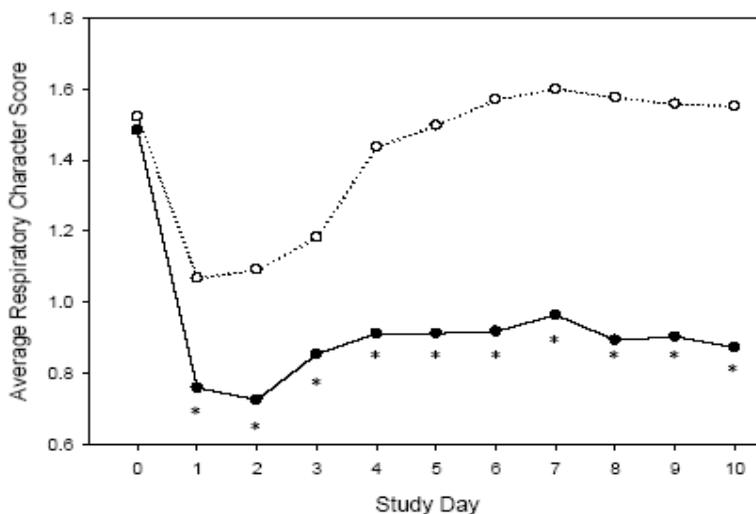
• represent the average respiratory character score for the Gamithromycin treated group
o represent the average respiratory character score for the Saline injected group
* denotes a statistically significant difference (p < 0.05)

treated with gamithromycin to cattle treated with saline. A randomized complete block design was applied for the randomization using the **PROC PLAN™** procedure of **SAS®** Version 8.2.

Treatments

1. Group 1-- Gamithromycin (15.0% w/v) injectable solution (**ZACTRAN®**) was administered on Day 0 by subcutaneous injection at 6.0 mg/kg bodyweight (2.0 mL/50 kg body weight) administered to the nearest 0.1 mL.

2. Group 2-- Sterile saline for injection (0.9% sodium chloride), administered at 2.0 mL/50 kg body weight administered to the nearest 0.1 mL.

Animal ear tags were used to verify the identity and treatment assignment of each animal. Each dose was calculated by referring to spreadsheets showing each animal's body weight on Day 0, which was converted from pounds to kilograms and verified against the dose chart provided in the protocol. Body weights in kilograms were either rounded up to the next higher kilogram or rounded to the nearest kilogram (whether higher or lower). Treatments were adminis-

tered as a single dose on Day 0 in the neck in front of the shoulder on the side opposite the site of vaccine administration. No more than 10 mL was given in an injection site.

Animal Management

Cattle were maintained in open-air pens with floors of dirt and concrete (Site 1), grass and sand (Site 2), or dirt (Sites 3 and 4) that were of standard North American feedlot design. Cattle were penned by replicate (comingled) following allocation until the final clinical observation, unless they were removed from their pen due to health problems. Multiple replicates were housed within each pen. Allocated floor space ranged from 67 to 303 ft2 per animal. Straw was used for bedding at Site 1. No bedding was used at other study sites. No environmental controls were applied.

Animals had free access to feed and water, including free choice grass hay or an alfalfa/grass hay mix. Additionally, a mixed feed containing lasalocid was fed to cattle in Site 1 (up to 4 lb per head per day) and Site 2 (ad libitum). A commercial, high-fiber, pre-conditioner/growing ration was fed in addition to the hay at Site 3 (8-10 lb per

Table 2. Summary of treatment successes and failures for feedlot cattle treated with gamithromycin or saline by site and overall

Site	Treatment	Number of treatment successes (%)	Number of treatment failures (%)
1	Gamithromycin	70 (78)	20 (22)
	Saline	10 (22)	35 (78)
2[a]	Gamithromycin	55 (47)	62 (53)
	Saline	18 (31)	41 (69)
3[b]	Gamithromycin	70 (82)	15 (18)
	Saline[c]	6 (14)	37 (86)
4[c]	Gamithromycin	14 (40)	21 (60)
	Saline	2 (11)	16 (89)
Overall	Gamithromycin	209 (64)*	118 (36)
	Saline	36 (22)	129 (78)

Treatment failure = clinical signs of BRD as defined by the following criteria: Days 4–9 post-treatment: depression score >1 OR respiratory character score > 1, AND rectal temperature of $\geq 40°C$; clinical signs as defined by the following scoring criteria on Day 10 post-treatment: Depression score >1, OR respiratory character score >1, OR rectal temperature of $\geq 40°C$.

[a]Excludes one animal removed inadvertently and therefore excluded from analysis
[b]Excludes two animals removed for non-BRD conditions and one animal that died from BRD prior to treatment and therefore was excluded according to the protocol
[c]Excludes one animal removed for non-BRD conditions
*$P<0.05$ vs. the saline group

head per day) and Site 4 (ad libitum). Fresh water from farm wells was available ad libitum through automatic waterers throughout the study.

A viral respiratory vaccine containing antigens for IBR, BVD, PI3, and BRSV (**Reliant ® 4**, Merial, Duluth, GA) and an endectocide (**Ivomec®** Pour-On for Cattle, Merial) were administered at processing. No antibiotics (except for the study drug) or vaccines containing antigens/toxins/toxoids of M. haemolytica, P. multocida, Histophilus somni, and/or Mycoplasma bovis were administered during the study.

When in the opinion of the attending veterinarian a moribund animal was unlikely to recover, the animal was humanely euthanized.

Primary Efficacy Endpoints

Each enrolled animal was assessed daily beginning on Day 0, prior to treatment, through Day 10. All persons performing all post-treatment evaluations were masked to the treatment assignment of the animals. The Monitor and persons administering treatments knew the treatment assignment of the animals.

From Days 1 to 10, animals were observed at approximately the same time of day (per local practice; typically in the morning.). The following scales for scoring depression and respiratory character were used for the study:

Depression

• 0 = Normal; nothing unusual in animal's attitude.

• 1 = Mild depression (somewhat slow coming to feed bunk, but did eat).

• 2 = Moderate depression (slight head/ears drooping, reluctant to move about, reluctant to come to the feed bunk).

Table 3. *Summary of mortalities attributed to BRD by study and overall showing BRD pathogens isolated from cattle that died*

Study	Treatment	Number of mortalities[a]	*Pasteurella multocida*	*Mannheimia haemolytica*	*Histophilus somni*	*Mycoplasma bovis*[b]
1	Gamithromycin	1	0	1	0	0[b]
	Saline	2	1	2	0	0[b]
2	Gamithromycin	1	0	1	0	1
	Saline	1	0	1	0	1
3	Gamithromycin	0	1	1	0	0
	Saline	8	4	8	2	0
4	Gamithromycin	0	0	0	0	0
	Saline	3[c]	1	3	0	3
TOTAL	Gamithromycin	2 (0.6%)	1	3	0	0
	Saline	14 (8.5%)	6	13	2	6

[a]*All deaths occurred on or after Day 1.*
[b]*Mycoplasma isolated, but not identified to species*
[c]*Two of the saline-treated calves at this study site became moribund and were humanely euthanized on Day 1 or 2; the third calf died on Day 4*

• 3 = Severe depression (pronounced head/ear droop; very reluctant to move).
• 4 = Moribund (recumbent).
Respiratory Character
• 0 = Normal: no abnormal respiratory symptoms present. Respiratory rate and effort were appropriate for the environment.
• 1 = Mild respiratory distress; serous nasal or ocular discharge and/or cough.
• 2 = Moderate respiratory distress: mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
• 3 = Severe respiratory distress: marked increase in respiratory rate or effort including one or more of the following: open mouth breathing, abdominal breathing, or extended head.

Rectal temperatures were measured and recorded daily for all enrolled animals from Day 0 to Day 10.

Treatment failures were defined as cattle not responding to treatment based on one of the following:

1. Mortality attributed to BRD from post-treatment Days 1 to 10 (confirmed by the presence of gross signs of BRD at necropsy); 2. Clinical signs of BRD as defined by the following criteria during Days 4-9 post-treatment period (clinical signs of BRD from days 1 through 3 did not constitute a treatment failure in these tudies):
• Depression score >1, OR
• Respiratory character score > 1, AND
Rectal temperature of $\geq 40^{\circ}$C; On Day 10, cattle demonstrating BRD clinical signs as defined by the following scoring criteria:
• Depression score >1, OR
• Respiratory character score >1, OR
• Rectal temperature of $\geq 40^{\circ}$C;

Animals declared treatment failures, were removed from their pen and from the study. These animals were placed in a separate pen, rescue treated with another antibiotic and retained at the study site. Animals that died or were humanely euthanized during the study (Day 0 to Day 10) were necropsied by a veterinarian or person under veterinary supervision.

Other Efficacy Endpoints

Figure 3. *Summary of Rectal Temperatures*
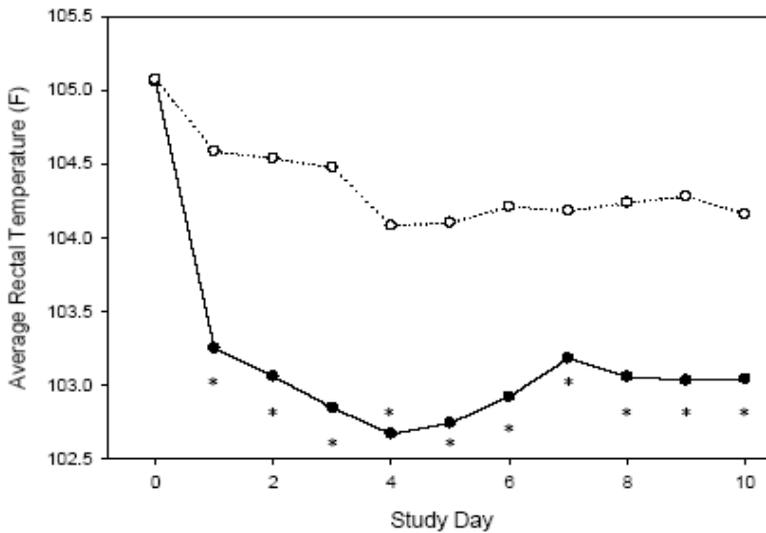
• *represent the average rectal temperature for the Gamithromycin treated group*
o represent the average rectal temperature for the Saline injected group
* *denotes a statistically significant difference (p < 0.05)*

Nasal swabs were collected immediately prior to treatment. Lung tissue sections and/or swabs from lung lesions and tracheal swabs were collected from cattle that died from BRD (confirmed by necropsy). All samples were submitted to the University of Wisconsin Veterinary Diagnostic Laboratory (Site 1), the Kansas State Veterinary Diagnostic Laboratory (Sites 2 and 3), or the University of Missouri Veterinary Medical Diagnostic Laboratory (Site 4) for culture of M. haemolytica, P. multocida, and H. somni, and identification of M. bovis by polymerase chain reaction (PCR).

Statistical Analysis

Data from all sites were combined for analysis. Clinical data for cattle that died before Day 10 were estimated using the last-observation-carried-forward method. Treatment was declared effective (successful) for gamithromycin if the proportion of treatment successes in that group on Day 10 was significantly higher (P≤0.05) than in the control group treated with saline. Numbers of treatment successes for the overall population were analyzed by a generalized linear model with a logit link function and a bino-

mial error distribution. Factors in the model included treatment as a fixed effect and site and treatment-by-site interaction as random effects.

Rectal temperatures were analyzed by a mixed model repeated measures analysis of variance. Factors included treatment, sampling day, and treatment-by-sampling day interaction as fixed effects and site, treatment-by-site interaction, sampling-day-by-site interaction, and treatment-by -- sampling-day-by-site interaction as random effects. Pre-treatment rectal temperature value was used as a covariate on post-treatment measurement. The covariate and the interaction of treatment and covariate were retained in the model as fixed effects because their associated F statistics were significant (P<0.05). The structure of the variance-covariance matrix was assumed to be a compound symmetry. A two-sided test was used at the significance level of 0.05 for all tests. All analyses were performed using the procedures of SAS® version 8.2.

RESULTS

Primary Endpoints

The percentage of overall treatment suc-

cesses for cattle treated with gamithromycin (64%) was significantly (P<0.05) greater than the group treated with saline (22%) (Table 2). Depression and respiratory character scores on Days 1 through 10 were significantly (P<0.05) lower in cattle treated with gamithromycin than in control cattle treated with saline (Figures 1 and 2). Mean rectal temperatures for cattle treated with gamithromycin were significantly (P<0.05) lower on Days 1 through 10, than for cattle treated with saline (Figure 3).

Over all studies, 14 deaths in the saline-treated group were attributable to BRD (8.5%) compared with two deaths (0.6%) in the gamithromycin-treated calves (Table 3). *Mannheimia haemolytica* was the most frequent pathogen isolated from cattle that died or were humanely euthanized.

No clinical adverse experiences occurred that were considered related to treatment.

DISCUSSION

Bovine respiratory disease occurs in cattle as a result of several complex factors, including the animal's susceptibility and the presence of pathogens under stressful conditions.[1,4,7] BRD remains the most common and expensive disease of feedlot cattle in the United States, considering the costs for increased labor, vaccinations, treatments, production, and death losses.[2,5,6]

Contributing factors to the immuno-suppression of the cattle include transport, which subjects the cattle to prolonged exposure to exhaust fumes, time without food or water, and overcrowding. Infectious agents of BRD are ubiquitous, and commingling of animals from different sources provides exposure to several infectious pathogens. Environmental risk factors include weather, exposure to dust, humidity, poor ventilation, high stocking density, and nutritional changes.[1,2,4-6,11-13]

Vaccination of feeder calves against BRD agents has been in practice for many years. However, many studies indicate that the use of vaccines has done little to reduce the incidence of BRD.[1,8,14] Often vaccines fail to provide desired protection in calves because of three major factors, including that calves are frequently comingled at sale barns, so that by the time they enter the feedlot where vaccines are routinely administered, they are already exposed to respiratory pathogens.

The second factor is that it is not possible to vaccinate against all the potential pathogens that could be present.

Thirdly, a stressed animal often has a compromised ability to develop an adequate vaccine response due to immunosupression from transport and handling stresses.

Several studies have shown that the therapeutic or prophylactic use of antibiotics is indicated for cattle with primary or secondary bacterial infections associated with BRD.[1,3,10,15-23] Antibiotics are routinely administered to all animals in a pen or lot, without determining the health status of individual animals beforehand, to prevent BRD development.[2,3,10,15,17,21,22] Therapeutically, antibiotics are administered to animals showing clinical signs of illness in an attempt to stop the infection.[16,18-20,23] Preventive or therapeutic antibiotic intervention may require repeated treatments of short-acting products or a single injection of a product that demonstrates persistent activity to prevent a relapse and to allow lung lesions to heal.

Azalide macrolides are particularly effective for treatment of bacterial respiratory infections because of excellent efficacy against the bacterial pathogens associated with BRD infections and their ability to achieve high concentrations in lung macrophages and in pulmonary epithelial lining fluid (PELF) of the bronchioles and alveolar airspaces, where BRD pathogens multiply and cause pathology.[9,24,25] Several macrolide antibiotics, including erythromycin, tylosin, tilmicosin, spiramycin, and tulathromycin are approved for treatment and or control of BRD in cattle in the United States and other countries.[25] Although these compounds are generally well absorbed and reach effective concentrations in lung tissue, many of them bind extensively to plasma proteins, which

restrict their extravascular distribution.[9,24,25] Therefore, some (eg, erythromycin) of these antibiotics require multiple doses for efficacy against BRD.

Gamithroymcin, an azalide member of the macrolide antibiotics, is currently licensed for treatment and control of BRD pathogens *M. haemolytica, P. multicida,* and *H. somni* in Canada and Europe.[7,9,10] Administered subcutaneously at 6 mg/kg (2mL/50kg), gamithromycin is well absorbed, and reaches maximum plasma concentrations within 1 hour after dosing.[9] However, plasma concentrations of gamithromycin are poor predictors of its clinical efficacy because distribution into lung tissue, the site of BRD infection, is rapid and extensive, reaching peak concentrations by 12 hours after subcutaneous injection.[26] Concentrations reach levels greater than the MIC90 for common BRD bacterial pathogens within 30 minutes.[26] Gamithromycin provides more active drug for distribution to lung tissue than other macrolide antibiotics because only 26% of the drug binds to bovine plasma protein.[7,9] From 1 to 15 days after injection, the ratio of drug in lung tissue ranged from 247 to 410 times the concentration measured in plasma. The volume of distribution (24.9 L/kg) after intravenous administration of gamithromycin to cattle is higher than that for erythromycin (0.79 L/kg), tilmicosin (2.65 L/kg), or tulathromycin (11.0 L/kg).[9] A single treatment of gamithromycin demonstrates excellent efficacy against BRD pathogens because of the prolonged concentrations in lung tissue resulting from a long elimination half-life (72 hrs) in those tissues.[7,9]

In the present study, cattle clinically ill from BRD treated with gamithromycin had significantly lower mean depression scores, respiratory character scores, and rectal temperatures on Days 1 through 10 than control cattle treated with saline providing at least a 10-day duration of efficacy. Mortality also was significantly lower for cattle treated with gamithromycin than for controls.

These results indicate that a single dose of gamithromycin at 6 mg/kg (2mL/50kg) is significantly effective as a treatment for feedlot beef cattle clinically ill from BRD.

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