Reasonable expectations for antibiotics in feedyards

Michael D. Apley, *DVM, PhD, DACVCP*, **Keith D. Dedonder,** *MS, DVM*
Department of Clinical Sciences, Kansas State University, Manhattan, KS 66506

Abstract

Use of the Number Needed to Treat (NNT) statistic allows for evaluation and communication of reasonable treatment outcome expectations in populations. The NNT value for a treatment estimates the number of animals which need to be treated in order to make an outcome difference in 1 animal. Evaluation of negative control studies for bovine respiratory disease suggests that the NNT values in high-risk calves for creating a treatment success, prevention of a mortality, and prevention of a clinical case through treatment for control of BRD are 2, 7, and 5, respectively. These values will obviously vary significantly in different clinical situations, but give reasonable expectations for the use of multiple antimicrobials in different groups of cattle over time.

Key words: beef, calves, feedyard, antimicrobial, treatment

Résumé

L'utilisation de la statistique du nombre de sujets à traiter permet l'évaluation et la dissémination des attentes concernant les résultats probables d'un traitement dans des populations. Pour un traitement donné, cette statistique permet d'estimer le nombre d'animaux qui doivent être traités afin d'obtenir une différence dans le résultat du traitement au niveau d'un animal. L'évaluation des études avec contrôle négatif portant sur le complexe respiratoire bovin suggère que le nombre de sujets à traiter chez les veaux à haut risque pour que le traitement permette un succès est de deux alors qu'il est de sept pour prévenir une mortalité et de cinq pour prévenir un cas clinique après un traitement pour contrôler le complexe respiratoire bovin. Ces valeurs vont bien sûr varier significativement dans différentes situations cliniques mais fournissent quand même un estimé raisonnable dans le contexte de l'utilisation d'antimicrobiens multiples dans différents groupes de bovins dans le temps.

Introduction

The pinnacle of the evidence scale is the randomized, masked, negative control, naturally occurring disease trial conducted in an environment with external validity for feedlot practice. The inclusion of a negative control allows separation of the true drug effect, as opposed to just reviewing clinical response data. The reason is that with few exceptions, the trials meeting these requirements I have reviewed contain animals that 1) respond without treatment in the control group, 2) display disease resolution in the treated group beyond what was displayed in the control group, and 3) animals that do not display disease resolution in the treated group. Therefore, we have some disease resolution in the untreated control group, and some failure to resolve the disease in the treated group.

Granted, these studies do not take into account the potential improved production performance of the successful cases in the treated group as opposed to the successful cases in the control group, but some type of clinical response is the basis for your clinical experience as far as drug effect, correct? In feedlot practice it is typical to monitor treatment outcomes and to use these data to constantly monitor therapeutic efficacy. How much of the monitored clinical outcomes are actually due to the drug?

A good statistic for evaluating drug effects in a population is the Number Needed to Treat (NNT). This is the number of animals which need to be treated with the drug to make a clinical outcome difference in 1 animal. It is calculated using the Attributable Reduction in Risk (ARR). For example, in a trial where 25% of the untreated controls were classified as treatment successes, and 75% of the treated group was classified as treatment successes, the ARR is 50% (75% – 25%). If the only 2 outcome options are success or failure it doesn't matter how you subtract, the difference is the same whether it's for the difference in successes or the difference in failures.

The NNT in this example would be 100%/50%, or 2, indicating that you need to treat 2 animals to make a difference in 1. Another way of looking at the example is that in every 4 treated animals there would be 1 response regardless of treatment (the 25% of untreated controls which are successes), 1 failure regardless of the treatment (the 25% of treated animals which were treatment failures), and 2 successes in the treated group which would have been failures in the control group (the ARR). Therefore, we made a difference in 2 out of 4, or 1 out of 2. We have to treat 2 to make a difference in 1, an NNT of 2.

NNT Analysis for Therapy and Control of Bovine Respiratory Disease

Table 1 summarizes treatment success rates in 30 bovine respiratory disease (BRD) therapeutic trials involving negative controls. The median NNT is 2; for every 2 animals treated for BRD in the overall population, 1 animal became a treatment success.

Table 2 summarizes reduction in mortality of treated cattle (case fatality) due to treatment for BRD in a subset of 24 of these 30 trials where mortality was reported. The median NNT for preventing a BRD mortality is 7; for every 7 animals treated for BRD in the overall population, 1 mortality was prevented in these study populations.

Table 3 summarizes the results of 12 different trials evaluating reduction in morbidity due to treatment for control of BRD. The median NNT for control of BRD is 5; for every 5 animals typical of these study populations which are treated for control of BRD in the overall population, 1 clinical case is prevented.

With few exceptions, these studies are pivotal dose-finding and clinical efficacy approval studies conducted under good clinical practices (GCP) guidelines and accepted in the approval process by the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM). These studies would predominantly represent high-risk calves. In my experience, the success/failure criteria used by the FDA/CVM result in a lower apparent clinical success rate than would be observed in typical feedlot practice. The mortalities have a fairly constant definition. The extrapolation of these results to low risk cattle would likely overestimate the effect of the antimicrobials due to an expected higher response rate in the untreated controls.

Ranking the efficacy of these antimicrobials based strictly on the lowest number needed to treat is inappropriate. I have concerns about comparing drugs based on separate negative-controlled clinical trials due to the potential for different factors influencing the negative control group's success rate in each trial, and these factors having different influences on the ability of the drug to respond. These factors could include age and weight of the cattle, clinical scoring criteria and interpretation, success/failure criteria, nutritional background, pathogens (susceptibility of bacterial pathogens and involvement of viral pathogens), and weather.

We should expect that resistant pathogens would result in the treatment success, mortality, and morbidity rates displayed by the untreated control groups in these studies. Treatment success rates in untreated cattle ranged from 0% to 57%, with a median of 23.9%. In contrast, treated success rates in treated cattle ranged from 51% to 92% with a median of 70.7%. The corresponding values for case fatality were a range of 2.5% to 48% with a median of 17.0% for untreated controls, and a range of 0% to 23.0% with a median of 1.0% for treated groups.

Conclusion

A large-scale view of the use of antimicrobials for the treatment and control of BRD in feedlot cattle helps to define reasonable expectations for efficacy in high-risk cattle. Clinicians recognize that these patterns may vary drastically based on cattle, environmental, and pathogen characteristics of a BRD challenge.

Acknowledgement

The author wishes to thank Dr. Keith DeDonder for his assistance in updating the references.

References

1. Efficacy trial. FOI Summary NADA 140-338, ceftiofur sodium sterile powder approved for the treatment of bovine respiratory disease (shipping fever, pneumonia). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
2. Dose response study. FOI Summary NADA 140-338, ceftiofur sodium sterile powder approved for the treatment of bovine respiratory disease (shipping fever, pneumonia). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
3. Dose response study. FOI Summary NADA 140-338, ceftiofur sodium sterile powder approved for the treatment of bovine respiratory disease (shipping fever, pneumonia). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
4. Multi-location clinical trial. FOI Summary NADA 140-338, ceftiofur sodium sterile powder approved for the treatment of bovine respiratory disease (shipping fever, pneumonia). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
5. Field study. FOI Summary NADA 141-209, ceftiofur crystalline free acid approved for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
6. Efficacy trial. FOI Summary NADA 141-063, florfenicol approved for treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
7. Field study. FOI Summary NADA 141-063, florfenicol approved for treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
8. Dose selection studies. Supplemental FOI Summary NADA 141-063, florfenicol approved for subcutaneous administration for the treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
9. FOI Summary NADA 141-265, multi-center evaluation of clinical efficacy of florfenicol in naturally occurring BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.

Table 1. Results of 30 trials evaluating treatment success of bovine respiratory disease therapy in cattle as evidenced by Attributable Reduction in Risk (ARR) and Number Needed to Treat (NNT).

Drug	Reference	Year	Study duration (days)	N treated (controls)	Treated success (%)	Control success (%)	P-value	ARR	NNT
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	1	Approved 1988	28	42 (42)	71.0%	55.0%	≤ 0.05	16.0%	6
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	2	Approved 1988	28	44 (44)	66.0%	45.0%	LSD = 17 (P = 0.05)	21.0%	5
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	2	Approved 1990	28	44 (44)	59.0%	45.0%	LSD = 17 (P = 0.05)	14.0%	7
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	3	Approved 1988	28	47 (47)	51.0%	39.0%	LSD = 17 (P = 0.05)	12.0%	8
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	3	Approved 1988	28	47 (47)	51.0%	39.0%	LSD = 17 (P = 0.05)	12.0%	8
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	4	Approved 1988	28	201(204)	69.0%	57.0%	LSD = 8.8 (P = 0.05)	12.0%	8
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	4	Approved 1988	28	201(204)	69.0%	57.0%	LSD = 8.8 (P = 0.05)	12.0%	8
Ceftiofur Crystalline Free Acid 6.6 mg/kg SC in ear	5	Approved 2003	14	54 (54)	70.4%	54.7%	NR	15.7%	6
Florfenicol 20 mg/kg IM 48 hours apart	6	Approved 1996	28	25 (25)	72.0%	24.0%	≤ 0.05	48.0%	2
Florfenicol 20 mg/kg IM 48 hours apart	7	Approved 1996	15	54 (41)	62.0%	12.0%	≤ 0.05	50.0%	2
Florfenicol 20 mg/kg IM 48 hours apart	8	Approved 1998	12	50 (25)	84.0%	20.0%	NR	64.0%	2
Florfenicol 40 mg/kg SC once	8	Approved 1998	12	50 (25)	90.0%	20.0%	NR	70.0%	1
Florfenicol 40 mg/kg SC once	8	Approved 1998	11	100 (50)	85.0%	16.0%	NR	69.0%	1
Florfenicol 40 mg/kg SC once	8	Approved 1998	11	100 (50)	53.0%	18.0%	NR	35.0%	3
Florfenicol 40 mg/kg SC once	9	Approved 2008	11	123 (122)	71.7%	42.9%	0.0162	28.8%	3
Enrofloxacin 2.5 mg/kg SC daily for 5 days	10	Approved 1996	15	12 (12)	92.0%	0.0%	≤ 0.05	92.0%	1
Enrofloxacin 5.0 mg/kg SC daily for 5 days	10	Approved 1998	15	12 (12)	58.0%	0.0%	≤ 0.05	58.0%	2
Enrofloxacin 2.5 mg/kg SC daily for 3-5 days	11	Approved 1996	28	296 (149)	74.0%	23.0%	≤ 0.05	51.0%	2
Enrofloxacin 5.0 mg/kg SC daily for 3-5 days	11	Approved 1998	28	95 (50)	54.0%	20.0%	≤ 0.05	34.0%	3
Enrofloxacin 7.5 mg/kg SC once	12	Approved 1996	28	302 (154)	64.0%	8.0%	≤ 0.05	56.0%	2
Enrofloxacin 12.5 mg/kg SC once	12	Approved 1998	28	102 (50)	81.0%	14.0%	≤ 0.05	67.0%	1
Danofloxacin 6 mg/kg IM twice 48 hours apart	13	Approved 2002	10	158 (80)	87.3%	28.3%	≤ 0.05	59.0%	2
Tulathromycin 2.5 mg/kg SC once	14	Approved 2005	14	314 (160)	78.3%	23.5%	0.002	54.8%	2
Gamithromycin 6 mg/kg SC once	15	Approved 2011	10	497	58.0%	19.0%	0.03	39.0%	3
Gamithromycin 6 mg/kg SC once	16	Approved 2012	10	121 (121)	74.4%	24.0%	<0.001	50.4%	2
Gamithromycin 6 mg/kg SC once	16	Approved 2012	10	130 (130)	67.4%	46.2%	0.002	21.2%	5
Tildipirosin 4 mg/kg SC once	17	Approved 2012	14	300 (300)	76.3%	32.0%	0.003	44.3%	2
Danofloxacin 8 mg/kg SC once	18	Approved 2011	10	160 (80)	83.1%	40.0%	0.0222	43.1%	2
Tulathromycin 2.5 mg/kg SC once	19	Published 2005	14	320 (160)	78.4%	23.8%	≤ 0.0001	54.6%	2
Tilmicosin 10 mg/kg SC once	19	Published 2005	14	320 (160)	65.0%	23.8%	≤ 0.0001	41.2%	2
Median					70.7%	23.9%		43.7%	2

Table 2. Results of 24 trials evaluating case fatality of bovine respiratory disease therapy in cattle as evidenced by Attributable Reduction in Risk (ARR) and Number Needed to Treat (NNT) to prevent a mortality.

Drug	Reference	Year	Study duration (days)	N treated (controls)	Treated mortality (%)	Control mortality (%)	P-value	ARR	NNT
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	1	Approved 1989	28	42 (42)	7.1%	31.0%	≤ 0.05	-23.9%	4
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	2	Approved 1989	28	44 (44)	16.0%	41.0%	LSD = 14 (P = 0.05)	-25.0%	4
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	2	Approved 1991	28	44 (44)	9.0%	41.0%	LSD = 14 (P = 0.05)	-32.0%	3
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	3	Approved 1988	28	47 (47)	23.0%	38.0%	LSD = 15 (P = 0.05)	-15.0%	7
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	3	Approved 1988	28	47 (47)	23.0%	38.0%	LSD = 15 (P = 0.05)	-15.0%	7
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	4	Approved 1988	28	201(204)	7.0%	25.0%	LSD = 6.1 (P = 0.05)	-18.0%	6
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	4	Approved 1988	28	201(204)	3.0%	25.0%	LSD = 6.1 (P = 0.05)	-22.0%	5
Florfenicol 20 mg/kg IM 48 hours apart	6	Approved 1996	28	25 (25)	4.0%	48.0%	≤ 0.05	-44.0%	2
Florfenicol 20 mg/kg IM 48 hours apart	7	Approved 1996	15	54 (41)	1.2%	34.0%	≤ 0.05	-32.8%	3
Florfenicol 20 mg/kg IM 48 hours apart	8	Approved 1998	12	50 (25)	0.0%	8.0%	0.1081	-8.0%	13
Florfenicol 40 mg/kg SC once	8	Approved 1998	12	50 (25)	0.0%	8.0%	0.1081	-8.0%	13
Florfenicol 40 mg/kg SC once	8	Approved 1998	11	100 (50)	0.0%	14.0%	0.0003	-14.0%	7
Florfenicol 40 mg/kg SC once	8	Approved 1998	11	100 (50)	1.0%	24.0%	0.0004	-23.0%	4
Enrofloxacin 2.5 mg/kg SC daily for 5 days	10	Approved 1996	15	12 (12)	0.0%	17.0%	≤ 0.05	-17.0%	6
Enrofloxacin 5.0 mg/kg SC daily for 5 days	10	Approved 1998	15	12 (12)	0.0%	17.0%	≤ 0.05	-17.0%	6
Enrofloxacin 2.5 mg/kg SC daily for 3-5 days	11	Approved 1996	28	296 (149)	0.0%	9.0%	≤ 0.05	-9.0%	11
Enrofloxacin 5.0 mg/kg SC daily for 3-5 days	11	Approved 1998	28	95 (50)	0.0%	14.0%	≤ 0.05	-14.0%	7
Enrofloxacin 7.5 mg/kg SC once	12	Approved 1996	28	302 (154)	3.0%	36.0%	≤ 0.05	-33.0%	3
Enrofloxacin 12.5 mg/kg SC once	12	Approved 1998	28	102 (50)	1.0%	12.0%	≤ 0.05	-11.0%	9
Danofloxacin 6 mg/kg IM twice 48 hours apart	13	Approved 2002	10	158 (80)	0.0%	2.5%	≤ 0.05	-2.5%	40
Tulathromycin 2.5 mg/kg SC once	14	Approved 2006	14	314 (160)	0.6%	5.6%	Not significant	-5.0%	20
Tildipirosin 4 mg/kg SC once	17	Approved 2012	14	300 (300)	0.0%	7.0%	0.003	-7.0%	14
Tulathromycin 2.5 mg/kg SC once	19	Published 2005	14	320 (160)	0.6%	5.6%	0.0011	-5.0%	20
Tilmicosin 10 mg/kg SC once	19	Published 2005	14	320 (160)	1.0%	5.6%	0.0035	-4.6%	22
Median					1.0%	17.0%		-15.0%	7

Table 3. Results of 12 trials evaluating morbidity after treatment for control of bovine respiratory disease in cattle as evidenced by Attributable Reduction in Risk (ARR) and Number Needed to Treat (NNT) to prevent a morbid animal.

Drug	Reference	Year	Study duration (days)	N treated (controls)	Treated mortality (%)	Control mortality (%)	P-value	ARR	NNT
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	1	Approved 1989	28	42 (42)	7.1%	31.0%	≤ 0.05	-23.9%	4
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	2	Approved 1989	28	44 (44)	16.0%	41.0%	LSD = 14 (P = 0.05)	-25.0%	4
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	2	Approved 1991	28	44 (44)	9.0%	41.0%	LSD = 14 (P = 0.05)	-32.0%	3
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	3	Approved 1988	28	47 (47)	23.0%	38.0%	LSD = 15 (P = 0.05)	-15.0%	7
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	3	Approved 1988	28	47 (47)	23.0%	38.0%	LSD = 15 (P = 0.05)	-15.0%	7
Ceftiofur sodium 1.1 mg/kg IM for 3 consecutive days	4	Approved 1988	28	201(204)	7.0%	25.0%	LSD = 6.1 (P = 0.05)	-18.0%	6
Ceftiofur sodium 2.2 mg/kg IM for 3 consecutive days	4	Approved 1988	28	201(204)	3.0%	25.0%	LSD = 6.1 (P = 0.05)	-22.0%	5
Florfenicol 20 mg/kg IM 48 hours apart	6	Approved 1996	28	25 (25)	4.0%	48.0%	≤ 0.05	-44.0%	2
Florfenicol 20 mg/kg IM 48 hours apart	7	Approved 1996	15	54 (41)	1.2%	34.0%	≤ 0.05	-32.8%	3
Florfenicol 20 mg/kg IM 48 hours apart	8	Approved 1998	12	50 (25)	0.0%	8.0%	0.1081	-8.0%	13
Florfenicol 40 mg/kg SC once	8	Approved 1998	12	50 (25)	0.0%	8.0%	0.1081	-8.0%	13
Florfenicol 40 mg/kg SC once	8	Approved 1998	11	100 (50)	0.0%	14.0%	0.0003	-14.0%	7
Florfenicol 40 mg/kg SC once	8	Approved 1998	11	100 (50)	1.0%	24.0%	0.0004	-23.0%	4
Enrofloxacin 2.5 mg/kg SC daily for 5 days	10	Approved 1996	15	12 (12)	0.0%	17.0%	≤ 0.05	-17.0%	6
Enrofloxacin 5.0 mg/kg SC daily for 5 days	10	Approved 1998	15	12 (12)	0.0%	17.0%	≤ 0.05	-17.0%	6
Enrofloxacin 2.5 mg/kg SC daily for 3-5 days	11	Approved 1996	28	296 (149)	0.0%	9.0%	≤ 0.05	-9.0%	11
Enrofloxacin 5.0 mg/kg SC daily for 3-5 days	11	Approved 1998	28	95 (50)	0.0%	14.0%	≤ 0.05	-14.0%	7
Enrofloxacin 7.5 mg/kg SC once	12	Approved 1996	28	302 (154)	3.0%	36.0%	≤ 0.05	-33.0%	3
Enrofloxacin 12.5 mg/kg SC once	12	Approved 1998	28	102 (50)	1.0%	12.0%	≤ 0.05	-11.0%	9
Danofloxacin 6 mg/kg IM twice 48 hours apart	13	Approved 2002	10	158 (80)	0.0%	2.5%	≤ 0.05	-2.5%	40
Tulathromycin 2.5 mg/kg SC once	14	Approved 2006	14	314 (160)	0.6%	5.6%	Not significant	-5.0%	20
Tildipirosin 4 mg/kg SC once	17	Approved 2012	14	300 (300)	0.0%	7.0%	0.003	-7.0%	14
Tulathromycin 2.5 mg/kg SC once	19	Published 2005	14	320 (160)	0.6%	5.6%	0.0011	-5.0%	20
Median					1.0%	17.0%		-15.0%	7

10. Dose regimen study. FOI Summary NADA 141-068, enrofloxacin approval for treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
11. Multi-location field study. FOI Summary NADA 141-068, enrofloxacin approval for treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
12. Multi-location field study. FOI Summary NADA 141-068, enrofloxacin approval for treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
13. Multi-location field trial. FOI Summary NADA 141-207, danofloxacin mesylate approved for the treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
14. Multi-location field trial. FOI Summary NADA 141-244, tulathromycin approved for the treatment of bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
15. Multi-location field trial. FOI Summary NADA 141-328, gamithromycin approved for the treatment of BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
16. Multi-location field trial. FOI Summary NADA 141-328, gamithromycin approved for the treatment of BRD associated with *Mycoplasma bovis* in beef and non-lactating dairy cattle. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
17. FOI Summary NADA 141-334, Multi-center field dose confirmation of the therapeutic efficacy of a single injection of tildipirosin in cattle undergoing a natural occurring outbreak of BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
18. FOI Summary NADA 141-207, supplemental approval, multicenter field dose confirmation of the therapeutic efficacy of a single injection of danofloxacin in cattle undergoing a natural occurring outbreak of BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
19. Kilgore WR, Spensley MS, Sun F, Nutsch RG, Rooney KA, Skogerboe TL. Therapeutic efficacy of tulathromycin, a novel triamilide antimicrobial, against BRD in feeder calves. *J Vet Ther* 2005; 6:143-153.
20. Multi-location field study. FOI Summary NADA 141-209, ceftiofur crystalline free acid approved for control of respiratory disease in cattle which are at high risk of developing BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
21. Multi-location field trial. FOI Summary NADA 141-244, tulathromycin approved for the control of respiratory disease in cattle at high risk of developing BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
22. Efficacy field trials. Supplemental FOI 141-063, florfenicol approval for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
23. Efficacy field trials. FOI Summary 141-143, oxytetracylcine injection 300 mg/ml approval for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease (BRD). Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
24. Effectiveness trial. Supplemental FOI Summary 140-929, tilmicosin approval for control of respiratory disease in cattle at high risk of developing BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
25. Efficacy field trial. FOI Summary NADA 141-328, gamithromycin approval for the control of bovine respiratory disease in cattle. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
26. Multi-location field trial. FOI Summary NADA 141-334, tildipirosin approval for the control of BRD in cattle at high risk for developing BRD. Accessed 7-24-2013 at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.
27. Kilgore WR, Spensley MS, Sun F, Nutsch RG, Rooney KA, Skogerboe TL. Clinical effectiveness of tulathromycin, a novel triamilide antimicrobial, for the control of respiratory disease in cattle at high risk for developing bovine respiratory disease. *J Vet Ther* 2005; 6:136-142.
28. Hibbard B, Robb EJ, Chester ST Jr, Dame KJ, Moseley WW, Bryson WL. Dose determination and confirmation for ceftiofur crystalline-free acid administered in the posterior aspect of the ear for control and treatment of BRD. *Vet Ther* 2002; 3:22-30.

ZACTRAN®
(gamithromycin)

150 mg/mL ANTIMICROBIAL
NADA 141-328, Approved by FDA
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.

INDICATIONS
ZACTRAN is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle. ZACTRAN is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle at high risk of developing BRD associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

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 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 Merial at 1-888-637-4251.

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 female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS
The effects of ZACTRAN on bovine reproductive performance, pregnancy, and lactation 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.

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%).
The effectiveness of ZACTRAN for the treatment of BRD associated with *M. bovis* was demonstrated independently at two U.S. study sites. A total of 502 cattle exhibiting clinical signs of BRD were enrolled in the studies. Cattle were administered ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline as a subcutaneous injection once on Day 0. At each site, the percentage of successes in cattle treated with ZACTRAN on Day 10 was statistically significantly higher than the percentage of successes in the cattle treated with saline (74.4% vs. 24% [$p<0.001$], and 67.4% vs. 46.2% [$p = 0.002$]). In addition, in the group of calves treated with gamithromycin that were confirmed positive for *M. bovis* (pre-treatment nasopharyngeal swabs), there were more calves at each site (45 of 57 calves, and 5 of 6 calves) classified as successes than as failures.
The effectiveness of ZACTRAN for the control of respiratory disease in cattle at high risk of developing BRD associated with Mannheim*ia haemolytica* and *Pasteurella multocida* was demonstrated in two independent studies conducted in the United States. A total of 467 crossbred beef cattle at high risk of developing BRD were enrolled in the study. ZACTRAN (6 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within one day after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for clinical success on Day 10 post-treatment. In each of the two studies, the percentage of successes in the cattle treated with ZACTRAN (86% and 78%) was statistically significantly higher ($p = 0.0019$ and $p = 0.0016$) than the percentage of successes in the cattle treated with saline (36% and 58%).

Marketed by Merial Limited
3239 Satellite Blvd., Duluth, GA 30096-4640 U.S.A.
Made in Austria

TAKE THE STRESS OUT OF BRD.

Target high-risk calves with ZACTRAN® (gamithromycin).

EXZACTLY THE RIGHT ANSWER FOR BRD.

Give subcutaneously at 2 mL/110 lbs.

With rising feed costs and tight margins, your clients are as stressed as their long-haul cattle. That's why they need ZACTRAN.

ZACTRAN delivers rapid onset[1] and 10-day duration[2] against the most prevalent causes of BRD in a single dose.[3,4] And most cattle stayed healthy with ZACTRAN, meaning fewer retreatments.[5] Talk to your clients about prescription ZACTRAN. It's exZACTly what you need to help them control BRD risk with one treatment.

ZACTRAN® (gamithromycin)

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.

[1] Sifferman RL, Wolff WA, Holste JE, et al. Field efficacy evaluation of gamithromycin for treatment of bovine respiratory disease in cattle at feedlots. *Intern J Appl Res Vet Med*. 2011;9(2):171-180.
[2] Lechtenberg K, Daniels CS, Royer GC, et al. Field efficacy study of gamithromycin for the control of bovine respiratory disease in cattle at high risk of developing the disease. *Intern J Appl Res Vet Med*. 2011;9(2):189-197.
[3] ZACTRAN product label.
[4] Kahn, CM. *Merck Veterinary Manual*. 10th edition. 2010:1319.
[5] Van Donkersgoed J, Merrill JK. A comparison of tilmicosin to gamithromycin for on-arrival treatment of bovine respiratory disease in feeder steers. *Bovine Practitioner*. 2012:46(1):46-51.

MERIAL
A SANOFI COMPANY