Approval Date: July 17, 1987

I. GENERAL INFORMATION:

A. NADA 139-472

B. Sponsor: Fermenta Animal Health Co.

C. Generic Name: tiamulin

D. Trade Name: DENAGARD Antibiotic Premix (Type A Medicated Article) DENAGARD 5 Medicated Premix (Type A Medicated Article) DENAGARD 10 Medicated Premix (Type A Medicated Article)

E. Marketing Status: Over the Counter (OTC)

F. Indications For Use

For the control of swine dysentery associated with *Treponema hyodysenteriae*susceptible to tiamulin. For increased rate of weight gain from weaning to 125 pounds body weight.

G. Dosage Form Premix

H. Route Of Administration Oral via feed

I. Recommended Dosages: 35 g/t for control of swine dysentery; 10 g/t for increased rate of weight gain from weaning to 125 lbs bwt.

II. EFFECTIVENESS

Effectiveness trials were conducted with tiamulin-medicated feeds prepared from three tiamulin premixes. These included the 25% tiamulin premix (DENAGARD), a formulation of tiamulin in cornstarch (TIAMUTIN®-Sandoz) and a tiamulin-extruded formulation (DYNAMUTILIN®-Squibb). The formulations have been shown to be equivalent on the basis of blood level bioequivalency studies.

A. Control Of Swine Dysentery

1. Pivotal Studies

The effectiveness of DENAGARD (tiamulin) premix for the control of swine dysentery associated with *Treponema hyodysenteriae* susceptible to tiamulin has been demonstrated by the results of three well-controlled laboratory and field trials conducted in three states with 512 pigs.

Dose determination trials with tiamulin at 20, 35 and 50 g/t were conducted in the laboratory (induced infection) and in the field (natural infections). No adverse reactions to tiamulin were observed in any of these trials. Individual trial summaries follow.

a. Test: MDA 012483

Study Type: Laboratory Dose Titration

Investigator:

T. J. Kennedy, Ph.D.
AEF Research, Inc.
5492 Kennedy Drive, Route 3
Waunakee, Wisconsin

The purpose of this trial of randomized block design was to evaluate tiamulin at 20, 35, and 50 g/t of feed vs. nonmedicated controls for the control of swine dysentery. Forty-eight crossbred pigs, 28 barrows and 20 gilts, averaging 34 pounds in weight were allotted 6 pigs per pen, 2 pens per treatment on the basis of weight and sex. All pigs were infected on test days 0 and 40 by feeding infective material (colonic tissue and contents) taken from pigs with clinical signs of swine dysentery. Medicated feed was self-fed from after infection on test day 0 to test termination on Day 63.

A tiamulin premix was used to prepare medicated feed in this trial.

Throughout the trial, pigs were observed and individually rated daily for general appearance, dehydration, diarrhea and presence of blood in feces. Weight gains and feed consumption were determined periodically throughout the test. All pigs were examined for the presence of treponemes on test days 1, 7, 14, 28, 42, and 56 by dark field microscopic examination of rectal swab material.

Results of this study were pooled with results from the other pivotal studies and statistical analysis appears later in this summary.

Table 1 MDA 012483

	Tiamulin, g/t			
Item	**0**	**20**	**35**	**50**
Number of pigs	12	12	12	12
Mortality, %	0	0	0	16.7
Average daily gain, lb	0.52	1.08	0.95	0.95
Average daily feed, lb	2.249	3.282	3.045	2.796
Gain/feed	0.239	0.332	0.316	0.343
Treponemes, % of exams	61.7	21.7	1.7	5.4
Days with bloody feces, %	22.7	0	0	0.8
Pig days with bloody feces, %	11.8	0	0	0.2
Days with diarrhea, %	68.8	28.2	0.8	0
Pig days with diarrhea, %	29.3	7.6	0.2	0
Average daily diarrhea score	0.624	0.118	0.002	0

No mortality due to swine dysentery occurred. Blood observed briefly, at 50 g/t was due to ulcerative colitis.

No adverse reactions to the test drug were observed.

b. Test: MDA 052783A-2

Study Type: Field Dose Titration

Investigator:
Eugene Nemechek, D.V.M.
905 Oak Forest Drive
Wilson, North Carolina 27893

This trial was conducted to evaluate continuous medication with tiamulin at 20, 35, and 50 g/t for the control of swine dysentery under practical conditions on a farm with a recent history of the disease.

A total of 240 crossbred pigs averaging 71.9 lb and approximately 11 weeks of age were used in this test of randomized block design. There were two replications of thirty pigs per treatment. Pigs were weighed and randomly allotted to pens and treatments were randomly assigned to pens within replications. Observations and ratings for diarrhea (0-3) and presence of blood in feces were recorded at least twice weekly. Pigs that died were weighed and a postmortem exam conducted to establish cause of death. After swine dysentery was confirmed present among non-medicated control pigs, the controls were fed feed containing tiamulin at 35 g/t for the final 3 weeks of the 57-day trial to reduce unnecessary animal loss.

No signs of toxicity or adverse reactions to tiamulin were observed in this trial.

The results of this trial were pooled with the other pivotal studies and statistical analysis appears later in this summary.

Table 2 Test MDA 052783A-2

	Treatment, g/t			
Item	**0***	**20**	**35**	**50**
Number of pigs allotted Deaths:	60	60	60	60
(1) Due to swine dysentery	2	0	0	0
(2) Total	6	4	2	0
Average daily gain, lb	1.57	1.64	1.62	1.76
Average daily feed, lb	4.63	4.62	4.38	4.81
Gain/feed	0.339	0.355	0.369	0.365
Average daily diarrhea score	0.4560	0.2599	0.1214	0.0628
Pig days with diarrhea, %	39.6	25.3	12.2	6.2
Test days with diarrhea, %	64.8	48.9	18.5	19.1
Pig days with bloody feces, %	2.8	0.9	0	0
Test days with bloody feces, %	24.5	9.4	0	0

* Tiamulin administered at 35 g/t for last three weeks of trial.

c. Test: MDA 041884

Study Type: Field Dose Titration

Investigator:
Marianne Ash, D.V.M.
P.O. Box 11
Camden, Indiana 46927

A field trial was conducted in a commercial swine operation in Indiana utilizing the tiamulin premix to evaluate continuous medication at 20, 35, and 50 g/t (active ingredient) in controlling swine dysentery in pigs housed in a facility in which the disease repeatedly occurred.

A total of 224 crossbred barrows and gilts average 50.2 lbs were randomly allotted to 8 pens in each of 2 similar adjacent rooms in a completely confined growing-finishing facility. Pens in these rooms were formed by solid partitions over a completely slotted floor.

In 3 of the 4 test treatments, pigs were continuously fed feed mixed to contain tiamulin at 20, 35, and 50 g/t over the total 13-week test period. The fourth treatment, nonmedicated controls, was maintained as such for five weeks after the start of the trial when swine dysentery was diagnosed present on the basis of clinical signs and observations at necropsy. Control pigs were then fed tiamulin at 35 g/t to test end.

Observations and ratings for diarrhea (0-3) and the presence of blood in the feces were recorded at least once weekly. Pigs which died were weighed and a postmortem examination performed to determine cause of death. Results of the 91-day trial are summarized in the following table.

No signs of adverse reactions or toxicity due to tiamulin were observed.

Results of this study were pooled with results from the other pivotal studies and statistical analysis appears later in this summary.

Table 3 MDA 041884

	Treatment, g/t			
Item	**0***	**20**	**35**	**50**
Number of pigs allotted Deaths:	56	56	56	56
(1) Due to swine dysentery	8	1	0	0
(2) Total	9	3	0	0
Average daily gain, lb	1.43	1.57	1.58	1.57
Average daily feed, lb	4.06	4.31	4.38	4.38
Gain/feed	0.352	0.364	0.361	0.359
Average daily diarrhea score	0.1824	0.0540	0.0094	0.0098
Pig days with diarrhea, %	9.38	2.81	0.52	0.73
Test days with diarrhea, %	25.0	32.4	1.5	6.1
Pig days with bloody feces, %	4.5	2.3	0.1	0.2
Test days with bloody diarrhea, %	17.6	17.6	1.5	3.0

* After five weeks on test, pigs were administered 35 g tiamulin/ton until test end.

d. Statistical Analysis

Statistical analysis of the most meaningful parameters consistent among the trials was conducted. The parameters were percent test days with diarrhea, percent pig days with diarrhea and average diarrhea scores.

a) Because of the number of 0 percentages and other small percentages, the arcsin of the square root of the proportion was used to transform the data. The value of 1/(4 X n) was substituted for zero values before transformation.
b) The use of Bartlett's test for homogeneity of variance found that the variances from location to location are homogeneous (P>.005) for all parameters. No weighted analysis was necessary.
c) An analysis of variance of the transformed data included effects for location, reps within location, treatment, treatment by location and error. For the three parameters analyzed, the treatment by location effect was always significant (P<.20) and was used to test the treatment effect, which were all significant (P<. 01).
d) Least square means derived from these analyses were subjected to model fitting, both linear plateau models as well as polynomial models. Two models, linear and Model III-2 (linear response from 0 - 35 gm/ton and plateau from 35 to 50 gm/ton), showed nearly equal characteristics of optimum fit for all parameters. Both models had R-squares greater than .93, all had coefficients that significantly contributed to the model and all had insignificantly little variation left to explain by fitting a different model. The linear model indicated the optimum dose to be 50 gm/ton whereas the Model III-2 indicated 35 gm/ton. Observing the means and graphs, it appeared that the response at 50 gm/ton was somewhere between the plateau and a straight linear relationship. It is not generally recommended to use pairwise testing in dose titration studies to determine the optimum dose, but in this case, the lack of significance between the 35 and 50 gm/ton levels (P>.40) would point to 35 gm/ton being a sufficient dose.

2. Corroborative Studies

Four trials involving 673 pigs are included as supporting evidence of effectiveness of tiamulin for the control of swine dysentery. These trials were conducted in Iowa (2), Missouri, and Wisconsin.

Tiamulin was tested at concentrations ranging from 20 to 50 g/t in the feed. Each trial included infected nonmedicated controls and 3 of the 4 trials included a positive control treatment (lincomycin).

The results of these trials support the conclusions reached in the pivotal efficacy studies.

No adverse reactions to tiamulin were observed in these trials.

Individual trial summaries follow.

a. Test: SR44 -214

Study Type: Laboratory Effectiveness

Investigators:
J. Hayden, D.V.M.
G. Thompson, Ph.D.
Gray Summit, Missouri

The purpose of this trial was to evaluate tiamulin at 35 g/t in feed for the control of swine dysentery. Mixed breed barrows and gilts averaging 72.4 lbs and about 15 weeks of age were randomly allotted 8 per pen to 12 pens. Three pens were nonmedicated controls; 9 pens were fed tiamulin at 35 g/t beginning after deliberate infection on Test Day 0. Pigs were weighed individually on Test Days -2, 49, and at test end on Day 70. Daily observations were made and pen groups rated for diarrhea and presence of bloody feces. Two pigs per pen (25%) were checked for spirochetes by dark field microscopic examination of rectal swabs taken on Test Days 0, 49 and 63. Bacterial culture of swab material for *T. hyodysenteriae* was also performed on Days 49 and 63 and on pigs with bloody feces on other days. Results of the 70-day trial are summarized below.

Table 4

Item	**Nonmedicated Control**	**Tiamulin 35 g/t**
Number of pens	3	9
Number of pigs	24	72
Average initial weight, lb	75.0	71.5
Percent mortality	25	0
Average daily gain, lb	1.24	1.86
Average daily feed, lb	4.63	5.97
Gain/feed	0.266	0.312
Average diarrhea score (0-3)	1.9333	0.6524
Test days with diarrhea, %	99.0	61.2
Test days with bloody feces, %	61.4	6.2
Rectal swabs culture+ for *T. hyo.*, %	33	7

No adverse reactions to tiamulin were observed.

b. Test: MDA 052783A

Study Type: Field Dose Titration

Investigators:
D.L. Weiss, D.V.M.
R.A. Howland, D.V.M.
Veterinary Clinic
R.F.D. #4
Fort Dodge, Iowa 50502

This field trial was conducted to evaluate continuous tiamulin medication at 20, 35, and 50 g/t for effectiveness in controlling swine dysentery under practical conditions on a farm with a history of the disease.

A total of 367 crossbred pigs, approximately half barrows and half gilts, and averaging 89 lbs were sorted by weight and origin and assigned to a total of 8 pens in an open-front Cargill-type finishing facility. There were two pens per treatment. The nonmedicated control treatment was maintained until about six weeks after the start of the trial when swine dysentery was diagnosed as present on the basis of clinical signs and confirmed present on the basis of postmortem examination of dead test pigs submitted to the state veterinary diagnostic laboratory. Control pigs were then treated with tiamulin in the drinking water at 60 ppm for 5 days and put on a diet containing tiamulin at 35 g/t to test end.

Observations and ratings for diarrhea (0-3) and the presence of blood in the feces were recorded at least twice weekly. Pigs that died were weighed and a postmortem examination performed to determine cause of death. Pleuropneumonia was a complicating factor in this trial.

Pigs were withdrawn from medication and removed from the trial on a pen-by-pen basis as they approached market weight or between 56 and 81 days after the start. Test results are summarized in the following table.

Continuous medication with tiamulin in the feed at 20, 35 and 50 g/t was effective in controlling signs of swine dysentery in this trial. Apparent weight gain response to levels of tiamulin in controlling swine dysentery may have been confounded by pneumonia in this trial.

No signs of adverse reaction or toxicity due to tiamulin were observed.

Table 5 MDA 052783A

	Treatment, g/t			
Item	**0***	**20**	**35**	**50**
Number of pigs allotted Deaths:	91	95	99	82
(1) Due to swine dysentery	2	0	0	0
(2) Total	8	7	3	1
Average daily gain, lb	1.43	1.30	1.40	1.67
Average daily feed, lb	5.41	5.12	5.43	6.96
Gain/feed	0.268	0.253	0.258	0.240
Average diarrhea score (0-3)	0.0259	0	0	0
Pig days with diarrhea, %	1.32	0	0	0
Test days with diarrhea, %	17.0	0	0	0
Pig days with bloody feces, %	0.9	0	0	0
Test days with bloody feces, %	9.8	0	0	0

* After 6 weeks, pigs were treated with tiamulin in the water followed by 35 g/t in the feed to test end.

c. Test: MDA 051884

Study Type: Field (Clinical) Effectiveness

Investigator:
Curt Daniels, D.V.M.
FIELD TRIALS
Mingo, Iowa 50168

A field effectiveness trial was conducted to evaluate tiamulin at 35 g/t for controlling a natural infection of swine dysentery an a commercial swine operation. Lincomycin at 40 g/t was used as a positive control treatment. One pen of nonmedicated controls was used to show that the disease was present in the facility. Swine dysentery was confirmed present in the control pigs on the basis of clinical signs observed during the 114-day trial and on the basis of gross lesions and the presence of *Treponema hyodysenteriae*in the colonic tissues of a control pig killed for necropsy at test end.

All pigs were rated for clinical signs of swine dysentery at least twice weekly throughout the test. Weight gains and feed consumption were determined on test days 65 and 114. Fecal material collected by rectal swabs from 5 pigs per pen on test days 1 and 65 and from all pigs on test day 114 were examined for the presence of spirochetes by microscopic examination and/or for *Treponema hyodysenteriae*by bacterial culturing. Results of determinations and observations made are summarized in the following table:

Table 6

	Nonmedicated Control	**Tiamulin 35 g/t**	**Lincomycin 40 g/t**
Number of pens	1	3	3
Total number of pigs	10	30	30
Average initial weight, lb	45.1	45.8	46.1
Mortality, %	0	0	0
Average daily gain, lb	1.549	1.533	1.529
Average daily feed, lb	4.90	4.81	4.82
Gain/feed	0.3161	0.3188	0.3170
Average diarrhea score (0-3)	0.2570	0.0000	0.500
Pig days with diarrhea, %	16.3	0.0	3.8
Test days with diarrhea, %	50.0	0.0	20.8
Test days with bloody feces, %	34.4	0.0	4.2
Exams for spirochetes positive/total exams(a)	4/20	3/60	6/60

(a)Combined results of exams on days 1, 65 and 114.

Tiamulin at 35 g/t was at least as effective as lincomycin at 40 g/t in controlling swine dysentery in this trial. No adverse reactions to tiamulin or to lincomycin were observed.

d. Test: MDA 051884A

Study Type: Field (Clinical) Effectiveness

Investigator:
T. J. Kennedy, Ph.D.
AEF Research, Inc.

5492 Kennedy Drive, Rt. 3
Waunakee, Wisconsin 53597
A total of 140 crossbred pigs averaging 132 pounds were allotted 14 per pen to 10 pens for this trial to compare tiamulin at 35 g/t with lincomycin at 40 g/t (positive control) for effectiveness in controlling a natural infection of swine dysentery in a hog farm operation. During the 38-day test, pigs were rated twice weekly for appearance, apparent dehydration and diarrhea and the presence or absence of bloody feces in the pens was recorded. All pigs were weighed at the start of the test and on Day 38, test end. Five pigs per pen were examined for treponemes by dark field microscopic examination of rectal swab material collected on Day 0 and again on Day 38. Results are summarized in the table below.

Table 7

	Nonmedicated Controls	**Tiamulin 35 g/t**	**Lincomycin 40 g/t**
Number pens	2	4	4
Mortality due to swine dysentery	1	0	1
Average daily weight gain, lb	1.015	1.586	1.506
Gain/feed	0.157	0.224	0.214
Average diarrhea score (0-3)	0.3490	0.0653	0.0922
Pig days with diarrhea, %	21.8	4.8	6.2
Test days with diarrhea, %	80.0	30.8	63.4
Test days with bloody feces, %	40.0	7.8	7.0
Pigs positive for treponemes, %: Day 0	80	85	70
Day 38	100	10	25

No adverse reactions to either tiamulin or lincomycin were observed.

Tiamulin at 35 g/t was at least as effective as the positive control drug, lincomycin at 40 g/t, in controlling swine dysentery in this field trial.

B. Increased Rate Of Weight Gain

1. Pivotal Studies (Three Trials: P-8-14-LT, P-9-3-NT, P-8-15-LT)

Three controlled trials with a total of 300 pigs, at an average initial weight of 23.5 lbs, were conducted in three states to demonstrate the effectiveness of tiamulin for increasing rate of weight gain to 125 lbs body weight. Tiamulin was evaluated at levels of 2.5 to 40 g/t in the diet. The 0, 10 and 20 g/t treatments were common to all three trials, while the 40 g/t level was tested in two trials.

Analyses of combined data from the three pivotal studies examined average daily gain and feed conversion values to market weight only for the 0, 10, 20, and 40 g/t treatment groups due to the imbalance in dose groups from location to location. Tiamulin at 10 g/t was found in the combined analysis to have significantly (p=.001) increased average daily gain. Feed conversion was not significantly different among treatments. The least squares means and standard errors derived from the combined analyses are as follows:

	ADG		**Feed/Gain**	
Dose Level gm/ton	**LS Means**	**s.e.**	**LS Means**	**s.e.**
0	1.393	.0215	3.237	.0437
10	1.501	.0215	3.227	.0437
20	1.433	.0215	3.2Q7	.0437
40	1.509	.0278	3.268	.0624

Data from trial P-9-3-NT, which included drug concentrations of 0, 2.5, 5, 10, and 20 g/t, were then analyzed separately to determine if levels of less than 10 g/t should be further titrated. Least squares means for average daily gains numerically increased from levels of 0 to 10 g/t, but there were no significant differences between control and any level tested in the study.

No adverse drug effects were observed in any of these trials. Individual trial summaries follow.

a. Test: P-8-14-LT

Study Type: Dose Titration

Investigators:
G. Cromwell, Ph.D.
T. Stahley
Department of Animal Science
University of Kentucky
Lexington, KY

This trial was conducted to evaluate tiamulin at 10, 20, and 40 g/t for effect on growth performance vs. non-medicated control pigs.

Eighty Yorkshire X Hampshire crossbred pigs averaging 32.5 lb were allotted on the basis of weight and sex to one of the 4 treatments listed below. There were 4 pens of 5 pigs per treatment in this test of randomized block design. A 16% protein corn-soy diet was fed to 125 pounds followed by a 12% protein corn-soy diet to market weight. A 25% tiamulin premix was used to prepare tiamulin-medicated feed which was fed to 125 pounds. Nonmedicated feed was fed after withdrawal of test drug. Average daily weight gain (ADG), feed consumption (ADF), and feed/gain values from test initiation to an average final weight of 208 lb are presented below.

Table 8

Treatment	No. Pigs	ADG, lb	ADF, lb	Feed/Gain
Nonmedicated control	20	1.48	4.84	3.27
Tiamulin, 10 g/t	20	1.62**	5.37*	3.34
Tiamulin, 20 g/t	20	1.56	5.20	3.35
Tiamulin, 40 g/t	20	1.63**	5.22	3.21

* P<.05 (vs. nonmedicated controls)
** P<.01 (vs. nonmedicated controls)

Tiamulin at all levels tested numerically increased rate of weight gain and feed consumption, but only at 40 g/t was feed conversion efficiency improved relative to nonmedicated controls.

No adverse reactions to tiamulin were observed.

b. Test: P-9-3-NT

Study Type: Dose Titration

Investigators:
G. Allee, Ph.D.
J. Riley
Eureka Testing
Manhattan, Kansas

The purpose of this trial was to evaluate tiamulin at 2.5, 5, 10 and 20 g/t vs. nonmedicated controls for effect on growth performance of swine.

One hundred-twenty crossbred pigs averaging 24 lbs were randomly assigned to pens by weight, sex and sire. There were 6 pigs per pen, 2 pens of barrows and 2 pens of gilts per treatment listed below. Treatments were randomly assigned to pens within replications in this test of randomized block design. Diets composed largely of grain sorghum and soybean meal were self-fed throughout with feeds formulated to contain

18, 16, and 14% protein fed from the start to 50 lbs, from 50 to 125 lbs and from 125 lbs to market weight (200-225 lbs), respectively.

Nonmedicated pigs were used as a negative control treatment. A 25% tiamulin premix was used to provide tiamulin at 2.5, 5, 10, and 20 g/t in feed which was self-fed to 125 lbs. Following withdrawal of test drugs, nonmedicated feed was fed to market weight. The results of this growth test are summarized below for the total period of feeding to market weight (average 210 lbs).

Table 9

Treament	No. Pigs	ADG, lb	Feed/Gain
Nonmedicated control	24	1.43	3.31
Tiamulin, 2.5 g/t	24	1.47	3.25
Tiamulin, 5 g/t	24	1.50	3.15
Tiamulin, 10 g/t	24	1.51	3.11*
Tiamulin, 20 g/t	24	1.45	3.13*

* P<.05 (vs. nonmedicated controls)

Tiamulin numerically improved the growth performance of pigs at all levels tested. Among pigs fed tiamulin, average daily gains and feed conversion efficiency improvements were largest at a level of 10 g/t.

No adverse drug effects were observed.

c. Test: P-8-15-LT

Study Type: Dose Titration

Investigator:
R. O'Kelley, Ph.D.
Animal Technautics
Terre Haute, Indiana

This trial was conducted to evaluate tiamulin at 10, 20, 30, and 40 g/t vs. nonmedicated controls for effect on growth performance of pigs.

One hundred mixed breed pigs averaging 14.4 lbs were randomly allotted by weight and litter to one of the 5 test treatments indicated below. There were 5 pigs per pen and 4 pens per treatment. A diet consisting largely of corn, milo and fish meal was fed to 125 lbs and a corn-soy diet fed thereafter to market weight at 200 lbs. A 25% tiamulin premix was used to prepare tiamulin medicated feed which was fed to 125 pounds body weight. Nonmedicated feed was fed after test drug withdrawal. Weight gain and feed conversion efficiency values from test initiation to the time pigs were 200 pounds are presented below:

Table 10

Treatment	No. Pigs	ADG,lb	Feed/Gain
Nonmedicated control	20	1.26	3.14
Tiamulin, 10 g/t	20	1.38	3.24
Tiamulin, 20 g/t	20	1.29	3.15
Tiamulin, 30 g/t	20	1.33	3.16
Tiamulin, 40 g/t	20	1.37	3.37

Numerical improvements in rate of weight gain were found with all medications tested, but none appeared to improve feed conversion efficiency. No apparent dose-related trends in ADG or Feed/Gain were evident among tiamulin treatments in this trial.

No adverse reactions to tiamulin were observed.

2. Supporting Studies (Two Trials: MDA011283, MDA121283)

   a. Test: MDA 011283

   Study Type: Dose Titration

   Investigator:
   V.C. Speer, Ph.D.
   Department of Animal Science
   Iowa State University
   Ames, Iowa

   The purpose of this trial was to evaluate tiamulin in the diet at 5, 10 and 20 g/t in growing-finishing pigs for effect on growth performance vs. a nonmedicated control treatment. A randomized block test was conducted with 4 pigs per pen, 6 pens per treatment. Barrows and gilts were penned separately. Crossbred pigs averaging 29.2 pounds were allotted on the basis of weight and sex and fed corn-soy type diets (16% then 14% protein) containing test medications continuously to market weight (average 202.3 lb). Growth performance during medication is summarized below.

Table 11

	Tiamulin, g/t			
Parameter (lbs)	**0**	**5**	**10**	**20**
Avg. daily wt. gain	1.375	1.446	1.508	1.484
Avg. daily feed consumption	4.83	4.90	4.84	4.86
Feed/gain	3.51	3.41	3.22	3.29

Tiamulin was effective in improving growth performance (P<.03) at all levels tested, with the greatest improvements in ADG and Feed/Gain observed at 10g/t.

No adverse effects due to tiamulin were observed.

b. Test: MDA 121283

Type: Dose Titration

Investigators:
Vernon B. Mayrose, Ph.D.
James R. Foster, Ph.D.
Department of Animal Science
Lilly Hall, Purdue University
West Lafayette, Indiana 47906

The purpose of this trial was to evaluate tiamulin in the diet at 5, 10, 20 and 40 g/t to growing-finishing pigs for effect on growth performance when fed continuously to market weight. A test of randomized block design with eight pigs per pen and four pens per treatment was used to evaluate the four levels of medication vs. a nonmedicated control treatment. Crossbred pigs averaging 37.2 lbs were allotted on the basis of weight, sex and litter and fed a corn-soy diet (18% followed by 16% and then 14% crude protein) to which appropriate levels of tiamulin were added. Pig weights and feed consumption were determined every two weeks to market weight. Pigs were removed from the trial as the average weight within replications was about 200 lbs. Growth performance during the medication period is summarized below:

Table 12

	Tiamulin, g/t				
Parameter (lbs)	**0**	**5**	**10**	**20**	**50**
Average initial wt.	37.1	37.2	37.4	37.3	37.2
Average final wt.	194.6	200.4	205.7	204.0	206.9
Average daily gain	1.499	1.555	1.607	1.589	1.616
Average daily feed	4.48	4.58	4.74	4.54	4.61
Feed/gain	2.99	2.95	2.95	2.86	2.85

Tiamulin significantly improved weight gain (P=.09) and feed conversion efficiency (p=.03) in this trial.

No adverse effects to tiamulin were observed.

III. SAFETY

The safety of DENAGARD (tiamulin) has been demonstrated in safety and effectiveness trials. A total of 1254 pigs received tiamulin in efficacy trials in which

tiamulin was fed at levels up to 50 g/t, for as long as 114 days. In none of the trials were any signs of toxicity or adverse reactions to tiamulin observed.

A series of well controlled studies are available to establish safety in the target species using both technical (unformulated) tiamulin and the water soluble (formulated) drug. These studies are discussed in the FOI Summary for DENAGARD Soluble Antibiotic NADA 134-644.

Experimental tiamulin premix formulations used in some efficacy and safety studies were shown in bioequivalence tests (cross-over blood level studies) to be equivalent to the formulation proposed for marketing.

A study to evaluate the safety of long term administration of tiamulin in the feed of swine was conducted by the Squibb Agricultural Research Center, E.R. Squibb and Sons, Inc., Three Bridges, New Jersey.

Male and female pigs averaging about 32 lbs. (14.8 kg) were fed feed containing tiamulin at 0, 40, 120 and 200 g/t continuously for 99 days when the pigs averaged about 206 lbs. (93.7 kg). These levels of medication are greater than 1, 3 and 5X the highest proposed use level of 35 g/t. There were 8 pigs per treatment level (32 total pigs) in the trial.

Weight gains and feed consumption were measured periodically throughout the test period. Blood samples and urine specimens were collected on Test Days -6, 0, 29, 57, 85 and 99. Urine samples were tested for pH, specific gravity, protein, ketones, glucose and sediment (microscopic exam). Blood glucose, calcium, phosphorus, sodium, potassium, blood urea nitrogen (BUN) and serum glutamic pyruvic transaminase (SGPT) were determined. Hematologic examinations included hematocrit, hemoglobin, red blood cell count, white blood cell count, differential white cell count, erythrocyte sedimentation rate, platelet count and clotting time.

At necropsy, liver, kidneys, adrenal, heart, spleen and thyroids were weighed. Histological examinations were made of the following tissues: spleen, liver, kidneys, thyroid/parathyroid, skeletal muscle, heart, lung, stomach (fundic and pyloric portions), duodenum, jejunum, ileum, cecum, colon and any tissue that did not appear normal on gross examination. Bone marrow smears taken at necropsy were also examined.

There were no drug-related changes in any of the clinical laboratory parameters tested. Organ weights were not different between treatments. The results of examinations for gross and microscopic pathology did not indicate any drug-related changes. Pigs fed tiamulin at 40, 120 and 200 g/t for 99 days gained weight more rapidly and efficiently observed on medicated pigs. No adverse reactions to the drug were observed.

IV. HUMAN SAFETY

A. Toxicity Tests

In addition to several short-term toxicity studies in mice, pigs, rats, rabbits, dogs, chickens, and turkeys with graded doses of tiamulin, the following pivotal

toxicity studies were conducted to demonstrate the safe and effective use of tiamulin: one-year feeding study in dogs, a lifetime feeding study in mice, a lifetime feeding study in rats, a three-generation reproduction and teratology study in rats, a rabbit teratology study, and fertility studies in male and female rats. These studies are discussed in detail in the FOI Summary for NADA 134-644 (DENAGARD Soluble Antibiotic).

B. Safe Concentration Of Residue

The tolerance for total tiamulin residues in edible tissue of swine is established in 21 CFR 556.738. For a discussion of the tolerance calculation, see the FOI Summary for NADA 134-644.

C. Metabolism And Residue Studies

1. Results of metabolism studies of tiamulin in rats and the target species are found in the FOI Summary for NADA 134-644 as well as a discussion of major metabolites, selection of the marker residue (8-alpha-hydroxymutilin), and the validated regulatory (GC) and confirmatory (GC-MS) methods for detection of the marker substance in the target tissue, swine liver.

   In accordance with the freedom of information provisions, a description of the regulatory method for detection and confirmation of residues of tiamulin is filed in the Feed Additives Analytical Manual on display in FDA's Freedom of Information Public Room (Room 12A-30), 5600 Fishers Lane, Rockville, MD 20857.

2. A withdrawal period of 2 days for the use of tiamulin in the control of swine dysentery was established in a residue depletion study in which 22 male and 22 female feeder pigs weighing 37.5 to 61.5 kg received feed containing tiamulin at the maximum proposed dosage of 35 g/t. The medicated diet was fed for 10 days to 16 pigs and for 18 days to the remaining 28 pigs. Both 10 and 18 day feeding provided steady-state residue data and residue data from both groups were used to determine the withdrawal period. The daily drug intakes were in the range from 1.7 to 2.1 mg/kg BW. Groups of 8 to 12 pigs were slaughtered at 2, 12, 16, 20 and 24 hours after cessation of medication. Liver samples were collected from each pig for the determination of 8-alpha-hydroxymutilin residues by an approved determinative method. The recovery of 400 ppb 8-alpha-hydroxymutilin in 5 fortified control liver samples ranged from 78.8 to 100% and averaged 86.5%. The mean values for marker residues of 8-alpha-hydroxymutilin in the target tissue (liver) of the medicated swine (males and females were equally represented) are shown in the following table.

Table 13 Residues of 8-alpha-hydroxymutilin in Swine Liver

Withdrawal Time (Hr)	Number of Animals	Mean ± SD ppb
2	8	447 ± 104
12	12	226 ± 85
16	8	256 ± 118
20	8	214 ± 66
24	8	175 ± 59

Based on these data, a withdrawal time of two days was assigned using the residue concentration corresponding to the 99% statistical tolerance limit with 95% confidence and the tolerance of 400 ppb for the marker residue.

3. A zero day withdrawal period for the use of tiamulin to increase rate of weight gain in pigs from weaning to 125 pounds body weight was established in a residue depletion study in which 12 male and 12 female feeder pigs weighing 25.0 to 31.5 kg received feed containing tiamulin at the level of 10 g/t for 10 days. The daily drug intakes were in the range from 0.5 to 0.6 mg/kg BW. Groups of 8 pigs were slaughtered at 8, 12 and 16 hours after cessation of medication. Liver samples were collected from each pig for the determination of 8-alpha-hydroxymutilin residues by the approved determinative method. The recovery of 100-400 ppb 8-alpha-hydroxymutilin in 13 fortified control liver samples ranged from 74.8 to 114.0% and averaged 96.6%. The mean values for marker residues of 8-alpha-hydroxymutilin in the target tissue (liver) of the medicated swine (males and females were equally represented) are shown in the following table.

Table 14 Residues of 8-alpha-hydroxymutilin in Swine Liver

Withdrawal Time (Hr)	Number of Animals	Mean + SD (ppb)
8	8	157 ± 92
12	8	141 ± 35
16	8	105 ± 35

Based on these data, a zero day withdrawal time was assigned using the residue concentration corresponding to the 99% statistical tolerance limit with 95% confidence and the tolerance of 400 ppb for the marker residue.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and demonstrate that DENAGARD (tiamulin) PREMIXES (Type A Medicated Articles) when used in swine feeds under the proposed conditions of use, are safe and effective for 1) the control of swine dysentery associated with *Treponema hyodysenteriae* susceptible to tiamulin; 2) increased rate of weight gain from weaning to 125 pounds body weight.

The basis of approval for human food safety for this original new animal drug application was based on contemporary standards. Several short-term toxicity studies in mice, pigs, rats, rabbits, dogs, chickens, and turkeys with graded doses of tiamulin, and a pivotal toxicity study were conducted to demonstrate the safe use of tiamulin: one-year feeding study in dogs, a liftime feeding study in mice, a lifetime feeding study in rats, a three-generation reproduction and teratology study in rats, a rabbit teratology study, and fertility studies in male and female rats. These studies are discussed in detail in the FOI Summary for NADA 134-644 (DENAGARD Soluble Antibiotic). The tolerance for total tiamulin residues in edible tissue of swine is established in 21 CFR 556.738. A residue depletion study for the swine dysentery indicated use established a 2-day withdrawal period. An additional residue depletion study for the increase in weight gain use established 0-day withdrawal.

The requirements of 21 CFR Section 558.15 were met for use of tiamulin in swine feed to 50 g/t. These requirements were met by determining that tiamulin fed to swine did not significantly increase the Salmonella shedding or increase the frequency of antibacterial drug resistance in Salmonella or indigenous coliform bacteria.

The agency concluded that the data submitted in support of this application have satisfied the human food safety requirements.

DENAGARD (tiamulin) PREMIXES (Type A Medicated Articles) are classified over-the-counter because adequate directions can be written for safe and effective use by non-veterinarians. Safe use has been demonstrated by data submitted to the application relative to the target animal, edible products from treated animals, and the drug's impact on the environment. The labeling carries appropriate warning, caution, and contraindication statements to support safe use.

Effective use by non-veterinarians can be expected because the swine producer has the ability to accurately judge the need for the control of swine dysentery and for the need to use DENAGARD (tiamulin) PREMIX for increased rate of weight gain from weaning to 125 pounds bodyweight. Mixing of the drug in swine feed is clearly described in the labeling and there is reasonable certainty that the conditions of use on the label will be followed.

VI. LABELING (attached)

1) DENAGARD® 10 Medicated Premix (Type A Medicated Article) package label
2) DENAGARD® 5 Medicated Premix (Type A Medicated Article) package label
3) Blue Bird Swine Feed (Type B) Medicated package label
4) Blue Bird COMPLETE SWINE RATION (Type C) Medicated (tiamulin 35 g/t) package label
5) Blue Bird COMPLETE SWINE RATION (Type C) Medicated (tiamulin 10 g/t) package label
6) DENAGARD® (Tiamulin) Antibiotic Premix (Type A Medicated Article) package label

Copies of these labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)

5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.