Approval Date: March 10, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-940

B. Sponsor

Pfizer Inc.
235 East 42nd Street
New York, N.Y. 10017

C. Proprietary Name

AVIAX®

D. Established Name

semduramicin sodium

E. Dosage Form

AVIAX® is a Type A medicated article (premix) containing 5.13% semduramicin sodium active ingredient.

F. Recommended Dosage and Route of Administration:

Thoroughly mix 1.0 lb AVIAX® Type A medicated article per 2000 lb of feed ingredients to provide 25 ppm (22.7 g) of semduramicin per ton of Type C finished broiler feeds. Feed continuously as the sole ration to broiler chickens.

G. Indication

For the prevention of coccidiosis in broiler chickens caused by *Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix* and *E. mivati/mitis*.

II. EFFECTIVENESS

A. Establishment of Dose

1. Field Isolate Battery Trials
   Investigator:

   Nigel Logan, Ph.D.
   Pfizer Animal Health Research
   Terre Haute, IN

   Five battery efficacy studies were conducted to determine the optimum dose of semduramicin. In four of these studies, single species inoculate (E. tenella, E. maxima, E. necatrix, or E. brunetti) were used. In the fifth study, a mixed inoculum containing E. acervulina, E. brunetti, E. mitis/mivati, E. maxima, E. necatrix and E. tenella was used.

Treatments consisted of non-infected, non-medicated control; infected, non-medicated control; and infected medicated treatments of 20, 25 or 30 ppm semduramicin. A summary of the data is given in Tables 1-4.

On the basis of this series of battery dose titration studies, it can be concluded that semduramicin is an effective anticoccidial against the 6 pathogenic species of Eimeria named and that the optimum dose is 25 ppm. Reduced average weight gains were observed at 30 ppm.

TABLE 1 % WEIGHT GAIN IMPROVEMENT OF MEDICATED BIRDS OVER INFECTED NON-MEDICATED BIRDS GIVEN VARIOUS OOCYST INOCULATE (48 birds/treatment)

Treatments	**ppm**	***E. tenella***	***E. maxima***	***E. necatrix***	***E. brunetti***	**Mixed**	**All Studies**
Non-Inf. Non-Med	0	9.6	35.2	100.4	26.3	51.4	39.1
Inf. Non-Med.	0	*	*	*	*	*	*
Inf. Semduramicin	20	5.2	19.9	100.2	16.1	37.3	30.0
Inf. Semduramicin	25	7.5	22.8	102.7	16.7	33.5	30.9
Inf. Semduramicin	30	4.1	17.8	95.5	16.3	29.6	27.4

* All treatments were compared to the Inf. Non-Med Treatment

TABLE 2 MORTALITY (%) AMONGST BIRDS GIVEN VARIOUS OOCYST INOCULATE (48 birds/treatment)

Treatments	**ppm**	***E. tenella***	***E. maxima***	***E. necatrix***	***E. brunetti***	**Mixed**
Non-Inf. Non-Med	0	0.0	0.0	0.0	0.0	0.0
Inf. Non-Med.	0	16.7	0.0	35.4	0.0	0.0
Inf. Semduramicin	20	6.3	0.0	0.0	0.0	0.0
Inf. Semduramicin	25	4.2	2.1	0.0	0.0	0.0
Inf. Semduramicin	35	2.1	0.0	0.0	0.0	0.0

TABLE 3 LESION SCORES OF BIRDS GIVEN SINGLE SPECIES INOCULATE (48 birds/treatment)

Treatments	ppm	*E. tenella*	*E. maxima*	*E. necatrix*	*E. brunetti*
Non-Inf. Non-Med	0	0.00	0.00	0.00	0.00
Inf. Non-Med.	0	2.96	3.00	3.69	3.13
Inf. Semduramicin	20	2.53	1.24	0.00	0.08
Inf. Semduramicin	25	1.88	1.06	0.00	0.05
Inf. Semduramicin	30	1.85	0.55	0.00	0.00

TABLE 4 MEAN LESION SCORES OF BIRDS GIVEN MIXED SPECIES INOCULUM (48 birds/treatment)

Treatments	ppm	MEAN INTESTINAL LESION SCORES - Upper	MEAN INTESTINAL LESION SCORES - Middle	MEAN INTESTINAL LESION SCORES - Lower	MEAN INTESTINAL LESION SCORES - Cecal
Non-Inf. Non-Med	0	0.00	0.00	0.00	0.00
Inf. Non-Med.	0	2.54	2.98	1.62	2.11
Inf. Semduramicin	20	0.57	1.78	0.02	0.75
Inf. Semduramicin	25	0.13	1.56	0.00	0.13
Inf. Semduramicin	30	0.04	0.99	0.00	0.11

B. Dose Confirmation

The efficacy of 25 ppm semduramicin was confirmed in a series of well-controlled studies which included battery tests against mono-specific isolates of all six Eimeria species and against mixed species isolates, and in a series of floorpen studies which evaluated continuous use of 25 ppm until 5 days before slaughter under conditions of severe coccidia infection.

1. Battery Studies
   Investigators:

   M.E. McKenzie, Ph.D.
   Pfizer Animal Health Research
   Terre Haute, IN

   Nigel Logan, Ph.D.
   Pfizer Animal Health Research
   Sandwich, Kent, England

In 42 battery studies conducted against a wide range of mono-specific field isolates of *E. tenella, E. acervulina, E. maxima, E. necatrix, E. brunetti*, and *E. mivati/mitis*, 25 ppm semduramicin consistently maintained weight gains, controlled lesions, and reduced mortality in comparison to infected, non-medicated controls. A summary of results is presented in Tables 5 through 10.

TABLE 5 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST *E. TENELLA* IN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, TEN TRIALS.

Treatment	ppm	Mean Weight Gain Grams	Mean Weight Gain % Difference	Mean Intestinal Lesion Scores	% Coccidiosis Mortality
Non-Inf. Non-Med	0	250.8	35.8	0	0.0
Inf. Non-Med.	0	184.7	**	2.92	19.0
Inf. Semduramicin	25	229.0	24.0	1.74	0.7

* 400 birds per treatment

** All treatments were compared to the Inf. Non-Med. Treatment

TABLE 6 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST *E. ACERVULINA* IN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, ELEVEN TRIALS.

Treatment	ppm	Mean Weight Grams	Meane Weight Gain % Difference	Mean Intestinal Lesion Scores	% Coccidiosis Mortality
Non-Inf. Non-Med	0	211.0	49.9	0.03	0.0
Inf. Non-Med.	0	144.1	**	3.23	0.2
Inf. Semduramicin	25	180.5	28.5	2.21	0.0

* 440 birds per treatment

** All treatments were compared to the Inf. Non-Med. Treatment

TABLE 7 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST E. MAXIMAIN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, EIGHT TRIALS

Treatment	ppm	Mean Weight Gain - Grams	Mean Weight Gain % Difference	Mean Intestinal Lesion Scores	% Coccidiosis Mortality
Non-Inf. Non-Med	0	245.8	46	<0.01	0.0
Inf. Non-Med.	0	168.3	**	2.61	0.3
Inf. Semduramicin	25	220.4	31	1.56	0.3

* 320 birds per treatment
** All treatments were compared to the Inf. Non-Med. Treatment

TABLE 8 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST E. NECATRIX IN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, THREE TRIALS.

Treatment	ppm	Mean Weight Gain - Grams	Mean Weight Gain % Difference	Mean Intestinal Lesion Scores	% Coccidiosis Mortality
Non-Inf. Non-Med	0	244.5	54.4	0.00	0.0
Inf. Non-Med.	0	158.4	**	2.68	20.8
Inf. Semduramicin	25	218.1	37.7	0.99	0.8

* 120 birds per treatment
** All treatments were compared to the Inf. Non-Med. Treatment

TABLE 9 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST E. BRUNETTI IN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, FOUR TRIALS.

Treatment	ppm	Mean Weight Gain - Grams	Mean Weight Gain - % Difference	Mean Intestinal Lesion Scores	% Coccidiosis Mortality
Non-Inf. Non-Med	0	246.8	56.3	0.00	0.0
Inf. Non-Med.	0	159.9	**	2.36	0.6
Inf. Semduramicin	25	239.0	51.4	0.41	0.0

* 160 birds per treatment
** All treatments were compared to the Inf. Non-Med. Treatment

TABLE 10 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST E. MIVATI/MITIS IN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, SIX TRIALS.

Treatment	Ppm	Mean Weight Gain - Grams	Mean Weight Gain - % Difference	Mean Intestinal Lesion Scores	% Coccidiosis Mortality
Non-Inf. Non-Med	0	209.6	66.6	0.00	0.0
Inf. Non-Med.	0	125.8	**	1.25	0.0
Inf. Semduramicin	25	184.8	46.9	0.99	0.0

* 240 birds per treatment

** All treatments were compared to the Inf. Non-Med. Treatment

A series of 15 studies was conducted in batteries to evaluate efficacy of 25 ppm semduramicin against 20 mixtures of *Eimeria* species in the proportions in which they were acquired by field isolation. Severe coccidiosis occurred among infected, non-medicated birds. Weight gain, lesion scores and mortality were significantly improved in birds medicated with 25 ppm semduramicin over infected, non-medicated controls. These studies confirmed that 25 ppm semduramicin was efficacious against mixed *Eimeria* species. Results are summarized in Table 11.

TABLE 11 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST MIXED *EIMERIA* SPECIES IN BROILER CHICKENS UNDER BATTERY CONDITIONS: SUMMARY OF WEIGHT GAIN, LESION SCORES AND MORTALITY, FIFTEEN TRIALS.

Treatment	PPM	Initial No. of Birds	Mean Weight Gain Grams	Mean Weight Gain % Diff.	Mean Intestinal Lesion scores Upper	Mean Intestinal Lesion Scores Middle	Mean Intestinal Lesion Scores Lower	Mean Intestinal Lesion Scores Cecal	% Mort*
Non-infected Nonmed.	0	600	262.6	62.8	<0.01	0.00	0.00	0.00	0.0
Infected Nonmed.	0	800	161.3	-	1.91	1.51	0.30	1.35	9.8
Infected Semduramicin	25	800	225.6	39.9	1.07	0.89	0.12	0.83	0.8

* Mortality Due to Coccidiosis

**All treatments were compared to the Infected Non-medicated treatment

2. Floorpen Studies
Investigators:

Elizabeth F. Illyes, M.S.
Pfizer Animal Health Research
Terre Haute, IN

Nigel Logan, Ph.D.
Pfizer Animal Health Research
Sandwich, Kent, England

Larry McDougald, Ph.D.
Georgia Poultry Research Inc.
Athens, GA.

Jeffrey N. Davidson, D.V.M., M.P.V.M.
Health Management Services
Tulare, CA.

To confirm efficacy under conditions more representative of commercial broiler production, highly replicated floorpen studies were undertaken. Studies were conducted according to a standardized protocol where one-day-old broiler-cross chickens were purchased from a commercial hatchery and vaccinated according to the test location's standard practice. Birds were administered semduramicin at 25 ppm and compared to infected, non-medicated groups.

The drug was evaluated against mixtures of E. tenella, E. acervulina and E. maxima in 11 studies and against mixtures of seven species of Eimeria in two studies. A total of 6451 semduramicin treated birds were included in the 13 studies. Assessed on the basis of lesion control, control of mortality and bird performance (weight gain and feed efficiency) over the 49 day grow out period, 25 ppm semduramicin provided control of coccidiosis. A summary of results is presented in Tables 12 through 15.

TABLE 12 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST MIXED INFECTIONS* OF *E. TENELLA, E. ACERVULINA* AND *E. MAXIMA* IN BROILER CHICKENS UNDER FLOORPEN CONDITIONS: SUMMARY OF LESION SCORES 6 DAYS FOLLOWING INOCULATION.

Treatments	ppm	MEAN INTESTINAL LESION SCORES - Upper	MEAN INTESTINAL LESION SCORES - Middle	MEAN INTESTINAL LESION SCORES - Lower	MEAN INTESTINAL LESION SCORES - Cecal
Non-Medicated	0	2.16	2.29	0.70	2.65
Medicated	25	1.82	1.35	0.17	1.65

* Inoculate contained known proportions of each species

TABLE 13 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST MIXED INFECTIONS* OF *E. TENELLA, E. ACERVULINA* AND *E. MAXIMA* IN BROILER CHICKENS UNDER FLOORPEN CONDITIONS: SUMMARY OF WEIGHT GAIN, FEED EFFICIENCY, MORTALITY AND TOTAL PRODUCTIVITY OVER 49-DAY GROWOUT.

Treatment	ppm	Mean Wt. Gain - Grams	Mean Wt. Gain - % Diff.	Feed Efficiency- F/G	Feed Efficiency - % Diff.	% Mortality - Coccidia	% Mortality - Other	Productivity - Kg/Pen**
Non-Medicated	0	1919.5	-	4.21	-	33.5	3.6	64.4
Medicated	25	2011.7	4.8	2.16	94.9	3.8	4.0	94.0

* Inoculate contained known proportions of each species.
** Total weight of live birds per pen at study termination.

TABLE 14 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST MIXED INFECTIONS* OF *E. TENELLA, E. ACERVULINA, E. MAXIMA, E. NECATRIX, E. BRUNETTI, E. MIVATI/MITIS* IN BROILER CHICKENS UNDER FLOORPEN CONDITIONS: SUMMARY OF LESION SCORES 6 DAYS FOLLOWING INOCULATION.

Treatments	ppm	MEAN INTESTINAL LESION SCORES - Upper	MEAN INTESTINAL LESION SCORES - Middle	MEAN INTESTINAL LESION SCORES - Lower	MEAN INTESTINAL LESION SCORES - Cecal
Non-Medicated	0	2.34	2.47	0.88	1.28
Medicated	25	2.29	1.40	0.29	1.09

* Inoculate contained known proportions of each species (*E. praecox* was also tested)

TABLE 15 ANTICOCCIDIAL EFFICACY OF SEMDURAMICIN AT 25 PPM AGAINST MIXED INFECTIONS* OF *E. TENELLA, E. ACERVULINA, E. MAXIMA, E. NECATRIX, E. BRUNETTI, E. MIVATI/MITIS* IN BROILER CHICKENS UNDER FLOORPEN CONDITIONS: SUMMARY OF WEIGHT GAIN, FEED EFFICIENCY, MORTALITY AND TOTAL PRODUCTIVITY OVER 49-DAY GROWOUT.

Treatment	ppm	Mean Wt. Gain - Grams	Mean Wt. Gain - % Diff.	Feed Efficiency- F/G	Feed Efficiency - % Diff.	% Mortality - Coccidia	% Mortality - Other	Productivity - Kg/Pen**
Non-Medicated	0	2153.9	-	2.38	-	19.2	2.7	79.6
Medicated	25	2274.8	5.6	2.08	12.6	3.6	3.4	100.4

* Inoculate contained known proportions of each species (*E. praecox* was also tested)
** Total weight of live birds per pen at trial termination

C. Commercial (Field) Studies

Investigators:
Mr. Thomas Hester
T & L Consulting Inc.
Morganton, NC

Mr. Michael Sims
Virginia Scientific Research Inc.
Harrisonburg, VA

Jerome Yates, Ph.D.
Campbell Institute for Research Technology
Fayetteville, AR

Three market-weight studies were conducted in U.S. commercial facilities in three different geographic regions to determine if semduramicin met commercial production expectations and was free from adverse side effects when fed to broilers raised according to contemporary production practices. In these studies semduramicin was also compared to approved products (salinomycin, halofuginone). All studies were conducted according to a standardized protocol. Large facilities located in North Carolina, Virginia, and Arkansas were chosen as test sites where two treatment groups could be raised in adjacent houses under directly comparable conditions. Semduramicin at 25 ppm was compared to reference drug A (salinomycin) in two studies and to reference drug E (halofuginone) in one study. The reference drug was the contemporary anticoccidial routinely used in the facility and one that had been selected by the producer from experience for its excellent control of coccidiosis and optimal broiler performance in the houses concerned.

There were no clinical signs of coccidiosis in any of the studies. Broilers that received semduramicin medicated feed showed no adverse reactions or side effects such as abnormal feathering patterns, wet droppings or increased incidence of leg weakness.

The performance of semduramicin-medicated broilers also compared favorably with that of broilers fed the contemporary anticoccidial drugs when assessed in terms of livability, total productivity, weight gain or feed efficiency. Results are presented in Table 16.

TABLE 16 EFFECTS OF SEMDURAMICIN AT 25 PPM ON PRODUCTIVITY OF BROILERS UNDER COMMERCIAL FIELD CONDITIONS

Location	Treatment	Days test (Days medicated)	Number of Birds	Live Birds (%)	Total Production (Kg)	Average Weight (Kg)	Feed Consumption (Kg)	Feed Eff. (F/G)
North Carolina	Semduramicin	45 (40)	16,400	96.4	28,390	1.80	54,132	1.91
North Carolina	Control A*	45 (40)	16,400	96.8	29,547	1.86	56,218	1.90
Virginia	Semduramicin	49 (44)	13,400	95.2	23,482	1.84	47,463	2.02
Virginia	Control A*	49 (44)	13,400	95.2	23,401	1.83	49,334	2.11
Arkansas	Semduramicin	41 (36)	24,000	97.1	33,669	1.44	62,505	1.86
Arkansas	Control E*	41 (36)	24,000	96.6	33,497	1.45	62,605	1.87
COMBINED STUDIES	Semduramicin	25	53,800	96.2	28,514	1.69	54,700	1.93
COMBINED STUDIES	Controls	-	53,800	96.2	28,815	1.71	56,052	1.96

* Reference drug(s) incorporated at their recommended use level: (A) salinomycin; (E) halofuginone

III. ANIMAL SAFETY

A. Safety Margin Studies

1. Safety in Mash Feed

Investigator:
Elizabeth F. Illyes, M.S.
Pfizer Animal Health Research
Terre Haute, IN.

The safety of feeding semduramicin to broilers at 25, 50 or 75 ppm was investigated in a 49-day floorpen study in which 360 male and 360 female broiler chickens were allotted to four treatment groups. Medicated mash broiler was fed for the first 44 days of a 49-day trial. Birds were examined daily for adverse clinical signs. Body weights and feed intake were recorded. Blood samples for hematological analyses were collected from a representative sample of birds from each pen at the beginning and end of the study. Gross pathologic and histopathologic post-mortem examinations were performed at study termination on birds pre-selected randomly from each treatment group.

At the 28 and 49-day observation points, the weight gain and feed efficiency of birds fed 25 ppm semduramicin were not significantly different from those of non-medicated birds. However, for birds fed 50 and 75 ppm levels, feed intake was

reduced by 28.2% and 47.6% respectively and weight gain by 37.1% and 63.7% respectively over the initial 28 days.

From Day 28 until the end of the study, tolerance to the drug improved and rates of feed consumption and weight gains improved markedly.

No adverse clinical signs were observed in any semduramicin-medicated birds regardless of dose, nor did medication result in increased mortality. There were no hematological abnormalities, no gross pathological or histopathological abnormalities, and no adverse effects on litter. A few 50 and 75 ppm medicated birds exhibited juvenile or thin feathering. Results are summarized in Tables 17 and 18.

TABLE 17 SUMMARY OF WEIGHT GAIN, FEED CONSUMPTION AND FEED EFFICIENCIES OF BROILER CHICKENS GIVEN 25, 50 AND 75 PPM SEMDURAMICIN IN MASH FEED

Treatment*	ppm	Mean Weight Gain - Day	Mean Weight Gain - Day 49	Feed Consumption grams - Day 28	Feed Consumption grams - Day 49	Feed Efficiency grams - Day 28	Feed Efficiency grams - Day 49
Non-Medicated	0	1006.7	2046.1	1529.2	4196.7	1.57	2.10
Semduramicin	25	993.6	2024.4	1494.4	4073.6	1.54	2.05
Semduramicin	50	633.3	1731.9	1097.4	3344.2	1.80	1.99
Semduramicin	75	365.5	1208.7	802.0	2500.0	2.21	2.11

* 180 Birds per treatment group.

TABLE 18 SUMMARY OF MORTALITY, CLINICAL, PATHOLOGIC, HISTOPATHOLOGIC AND HEMATOLOGICAL EFFECTS IN BROILER CHICKENS GIVEN 25, 50 AND 75 PPM SEMDURAMICIN IN MASH FEED

Treatment	% Mortality	Signs of Toxicity	Feathering	Litter Moisture	Hematology	Blood Chemistry
Non-Medicated	4.4	None	Normal	Normal	Normal	Normal
Semduramicin 25	2.2	None	Normal	Normal	Normal	Normal
Semduramicin 50	4.4	None	Abnormal*	Normal	Normal**	Normal
Semduramicin 75	2.8	None	Abnormal*	Normal	Normal**	Normal

* In <0.6% of 50 ppm and <1.7% of 75 ppm birds poorly feathered shoulders and breasts were observed.
** In a few 50 ppm and 75 ppm birds, hemoglobin values were within normal limits based on body weight but slightly depressed based upon age.

2. Safety in Crumbled Feed

Investigator:
Nigel B. Logan, Ph.D.
Pfizer Animal Health Research
Terre Haute, IN.

The effect of feeding 25, 50, and 75 ppm semduramicin in crumbled feed on the performance and livability of broiler chickens was investigated in a 49-day floorpen study in which 360 male and 360 female broiler chickens were allotted to four treatment groups. The birds received medicated feed for the first 44 days of a 49-day trial. Feed intake was recorded throughout the study and birds were weighed individually on days 28 and 49. No adverse clinical signs were observed in any semduramicin-medicated birds regardless of dose, nor did medication result in increased mortality. The weight gain and feed efficiencies of birds were unaffected by the inclusion of 25 ppm. The weight gains of birds receiving 50 or 75 ppm semduramicin were depressed by 19% and 46%, respectively, and feed efficiencies by 2% and 20%, respectively, compared to non-medicated birds. Results are summarized in Table 19.

TABLE 19 SUMMARY OF WEIGHT GAIN, FEED CONSUMPTION AND FEED EFFICIENCY AND MORTALITY OF BROILER CHICKENS GIVEN 25, 50 AND 75 PPM SEMDURAMICIN IN CRUMBLED FEED

Treatment*	ppm	Mean Weight Gain, g - Day 28	Mean Weight Gain, g - Day 49	Feed Consumption, g - Day 28	Feed Consumption, g - Day 49	Feed Efficiency - D 28	Feed Efficiency - D 49	% Mortality - Day 28	% Mortality - Day 49
Non-Medicated		1152.4	2672.2	1753.8	5004.1	1.54	1.92	5.6	9.4
Semduramicin	25	1129.2	2598.2	1720.7	4886.3	1.53	1.92	1.7	6.1
Semduramicin	50	812.4	2167.5	1404.0	4159.0	1.76	1.96	5.0	6.7
Semduramicin	75	437.4	1448.2	1074.2	3270.9	2.48	2.30	1.1	3.9

* 180 Birds per treatment group.

B. Safety in Other Animal Species

1. Turkeys

Investigator:
Nigel B. Logan, B.Sc., Ph.D.
Pfizer Animal Health Product Development
Sandwich, UK

The safety of semduramicin sodium at 25 ppm was evaluated when included in the feed of growing turkeys between 0 and 12 weeks of age.

Four hundred and eighty male and 480 female one-day old turkey poults were assigned to a control and a medicated group. The birds in the control group were fed non-medicated ration and the medicated group received semduramicin sodium at 25 ppm. The study was conducted for 12 weeks. The turkeys were observed daily for signs of toxicity. Feed consumption and mortality were

recorded throughout the experiment and they were weighed on days 0, 28, 56, and 84. There was no difference between the weight gain of birds receiving semduramicin sodium and the control group. The mortality levels were similar in both groups. No adverse reactions were observed in turkeys receiving semduramicin sodium at 25 ppm.

2. Horses

Investigator:
Nigel B. Logan, B.Sc., Ph.D.
Pfizer Animal Health Product Development
Sandwich, UK

The safety of semduramicin sodium at 25 ppm was evaluated when included in the feed of horses for 21 days. Two groups of six horses were included in the study. Six horses received non-medicated feed acting as a control group. The animals were weighed weekly and observed daily for signs of toxicity or adverse reactions. Blood samples were collected before and after the study period for biochemical and hematological analyses. No adverse clinical reactions were observed nor were there significant changes in any variables measured among the horses receiving semduramicin sodium.

C. Effects on Microbial Populations

1. Antimicrobial Resistance

Investigator:
D. Fagerberg, Ph.D.
Colorado Animal Research
Fort Collins, CO

A study was conducted to evaluate the effect of semduramicin sodium on the incidence and antimicrobial resistance of indigenous fecal coliforms.

Baseline antibiograms were determined from multiple fecal samples during a fourteen-day acclimation period for 24 individually caged non-medicated broiler chickens. Twelve of these birds then received semduramicin at 25 ppm continuously in the feed for an additional eight weeks. Antibiograms on ten coliform isolates per bird were determined weekly during the period of medication. Bacterial sensitivity to amikacin, ampicillin, carbenicillin, cefoxitin, chloramphenicol, gentamicin, kanamicin, nalidixic acid, streptomycin, sulfadiazine, tetracycline and trimethoprim/ sulfamethoxazole were determined. Based on a comparison to non-medicated birds, the administration of semduramicin had no effect on coliform resistance to antimicrobials.

2. Salmonella typhimurium Resistance/Shedding

Investigator:
D. Fagerberg, Ph.D.
Colorado Animal Research
Fort Collins, CO

A study was conducted to determine the effects of semduramicin in the diet of broiler chickens on the tissue levels, antimicrobial resistance and shedding of *S.*

typhimurium. Feed containing either semduramicin at 25 ppm, a commercial ionophore standard or no feed additive (non-medicated control) was administered *ad libitum* to groups of 12 chicks, five days after oral inoculation with viable *S. typhimurium*. A non-infected/non-medicated group (environmental control) was also maintained. Fecal samples were collected twice prior to the start of medication and 9 times during a subsequent 35-day treatment period for quantitation and/or detection of test-strain salmonellae. Antibiogram profiles of five isolates per bird were determined at two pre-treatment sampling days and five post-treatment sampling days. At the time of death or the end of the treatment period, liver, spleen and cecal contents were cultured for test salmonellae. Semduramicin had no statistically significant effect on either prevalence or duration of *Salmonella* shedding, on sequestration of salmonellae in tissues or on antimicrobial resistance.

IV. HUMAN FOOD SAFETY STUDIES

A. Toxicology

Unless otherwise specified, all testing was performed with bulk semduramicin sodium. The dosage levels cited below are given in terms of semduramicin activity. On a molecular weight basis, semduramicin represents approximately 97.5 % of semduramicin sodium. All pivotal testing was conducted in full compliance with the Good Laboratory Practice regulations (21 CFR 58).

All of the conventional toxicology and multiple-generation reproduction safety studies were conducted at the Pfizer Central Research facilities located at Groton, Connecticut. Genetic toxicology studies were conducted at both Pfizer Central Research, Groton, CT (Ames and Mouse Lymphoma) and at Hazleton Laboratories America, Inc., Kensington, MD (UDS).

The teratology/fetotoxicity studies were conducted at the Pfizer Central Research facilities at Amboise, France. The dog cardiovascular physiology work was conducted at Battelle Memorial Institute, Columbus, Ohio.

1. One Month Feeding Study in Rats

   Protocol No. 85-564-01 started 10/21/85 Semduramicin was administered in the diet to provide daily drug intake of 0, 0.14, 0.28, 0.56, 1.12, and 2.24 mg/kg to groups of 5 Long-Evans rats per sex for five weeks.

   Body weights and food consumption were monitored weekly and the inclusion rate in feed adjusted accordingly. Each animal was observed twice daily. Serum chemistry profiles were obtained before the initiation of treatment and at three points during treatment. All rats were sacrificed at the end of the trial and subjected to a gross necropsy. Kidney and liver weights were taken and selected major organs subjected to histopathological examination.

   The high dose (2.24 mg/kg/day) females showed depressed gain weight and by the end of the study weighed 14.7% less than controls. Histologically, one male and 1 female had centrilobular hepatocellular hypertrophy. A mild hepatic fatty change was observed in two 1.12 mg/kg males. The no observed effect level was 0.56 mg/kg/day.

2. One Month Feeding Study in Dogs

   Protocol No. 85-564-03 started 1/27/86 Four groups of two male and two female seven month old beagle dogs received semduramicin in feed to provide daily dosage levels of 0, 1, 2 or 4 mg/kg. Accurate dosage was assured through weekly body weight and daily food consumption monitoring. Each dog was observed at least twice daily. Evaluations made prior to and during the period of medication included: ECG, systolic blood pressure, ophthalmoscopy, serum chemistry, hematology, and urinalysis. All animals were subjected to a complete gross necropsy and samples of major organs taken for histopathologic examination. Progressive ataxia was observed in the high dose dogs along with elevations of CPK, SGOT and SGPT.

   The dose of 4 mg/kg produced effects ranging from temporary difficulty in standing and walking in two dogs to complete and permanent inability to stand in two other dogs. Elevations in the serum activities of CPK, SGOT and SGPT occurred in all dogs at the 4 mg/kg dose, and all dogs had microscopically apparent muscle degeneration, necrosis as well as neuropathy. Dogs receiving 2 mg/kg appeared clinically normal but all had degree of CPK elevations and, for one dog, SGPT and SGOT. One dog at the 2 mg/kg level had microscopic evidence of muscle degeneration and necrosis. The no observed effect level was 1 mg/kg/day.

3. Three Month Feeding Study in Rats

   Protocol No. 85-564-03 started 1/27/86 Four groups of two male and two female seven month old beagle dogs received semduramicin in feed to provide daily dosage levels of 0, 1, 2 or 4 mg/kg. Accurate dosage was assured through weekly body weight and daily food consumption monitoring. Each dog was observed at least twice daily. Evaluations made prior to and during the period of medication included: ECG, systolic blood pressure, ophthalmoscopy, serum chemistry, hematology, and urinalysis. All animals were subjected to a complete gross necropsy and samples of major organs taken for histopathologic examination. Progressive ataxia was observed in the high dose dogs along with elevations of CPK, SGOT and SGPT.

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4. One Year Feeding Study in Beagle Dogs

   Protocol No. 89-564-12 started January 1990 Groups of five male and five female beagle dogs received semduramicin via the feed to provide daily dose levels of 0.0, 0.1, 0.3 and 1.0 mg/kg for 373 consecutive days. Accurate dosing was assured through weekly body weight and daily food consumption monitoring. Each dog was observed daily for clinical signs and food consumption. Body

weights were recorded weekly. Ophthalmoscopic examinations, ECGs and measurements of blood pressure and various serum chemistry, hematology and urinalysis were made periodically. At trial termination, all dogs were sacrificed and subjected to a complete gross necropsy. Absolute weights were recorded for kidneys, liver and testes. Tissues from an extensive list of organs were fixed and examined histologically, including ultrastructural examinations of the retina.

In the 1.0 mg/kg group the following effects were observed: increase in systolic blood pressure, hyaline degeneration, fragmentation of the retinal rod and cone cell segments in both the tapetal and non-tapetal regions, and funduscopically visible, ring-shaped lesions which were histologically observed as areas of retinal detachment. Retinal alterations were observed in 5 out of 10 high dose dogs beginning 6 months after initiation of drug treatment. Sorbitol dehydrogenase values were increased in 9 out of 10 dogs in the high dose group. The no observed effect level was 0.3 mg/kg/day.

5. Teratology and Reproductive Toxicology

Three Generation Feeding Study in Rats Protocol No. 87-564-04 started 9/14/87

Semduramicin was administered via the diet to groups of 45 male and 45 female young adult Long-Evans rats to provide daily dose levels of 0, 0.25, 0.5 and 1.0 mg/kg. These rats constituted the F0 generation with males medicated for approximately 12 weeks and females approximately 2 weeks prior to cohabitation/mating. These dose levels were maintained throughout the study. The F0 generation was maintained until weaning of the F1a pups of which 25/sex/group were raised to maturity and mated twice to produce F2a and F2b litters. The F2a pups were sacrificed after weaning and the F2b pups subjected to behavioral tests at weaning. Twenty-five F2b pups per sex per treatment level were raised to maturity and mated to produce the F3 generation which was raised to weaning and sacrificed. Pregnancy rates, litter size and pup viability were monitored.

There were no drug effects on percentage of females which copulated, litter size or pup survivability and weight gain. Pregnancy rates for F1 animals in both the first and second mating were lower for the high and low dose groups compared to controls.

However, results for mating of F2 generation failed to confirm a correlation for decreased pregnancy rates and treatment. A drug related effect was observed in a 10-15% decrease in body weights for all the high dose dams (F0, F1 and F2b) during the lactation period. The no observed effect level for maternal toxicity and fetotoxicity was 0.5 mg/kg/day.

Fetotoxicity in Rats Protocol Nos. 88010 and 88011 started 01/19/88

Semduramicin was administered by gavage to groups of 20 inseminated rats for 10 days (day 6 through day 15 post-insemination) at daily dose levels of 0, 0.25, 0.5 and 1.0 mg/kg. Animals were observed for clinical signs daily, weighed periodically and had food consumption measured on days 3, 9 and 16. Hysterectomies were performed on day 20 post-insemination. All fetuses were weighed and examined for external and buccal anomalies. Half of each litter were

examined for visceral anomalies and the other half for skeletal anomalies and degree of ossification.

The food intake of 1 mg/kg females was reduced (2.7 % to 3.5%) before, during and after the treatment period. The high dose level induced a delay in maternal body weight gain during and after treatment period. There was also a decrease in the mean body weights of female fetuses in the high dose group. The no observed effect level for maternal and fetotoxicity was 0.5 mg/kg/day.

Fetotoxicity in Rats Protocol Nos. 88168 and 88169 started 12/27/88

A second rat fetotoxicity study was conducted using a protocol identical to that summarized above but with dose levels of 0, 1, 2 and 4 mg/kg/day.

At the 4 mg/kg level, 18 of 20 died during the treatment period. Embryomortality rate was significantly increased at 4 mg/kg when compared to controls. Ectopic testes were observed at the 4 mg/kg dose. At the intermediate dose of 2 mg/kg the females showed a weight gain of about 10% of the low dose animals and the controls. Fetal body weights were decreased at 2 and 4 mg/kg. Skeletal anomalies were observed at 4 mg/kg and ossification delays were observed at the 4 mg/kg and 2 mg/kg levels. The no observed effect level for maternal and fetotoxicity was 1.0 mg/kg/day.

Fetotoxicity in Rabbits Protocol Nos. 88012 and 88013 started 02/01/88

Semduramicin was administered by gavage to groups of 20 inseminated rabbits for 12 days (day 7 to day 18 post-insemination) at daily dose levels of 0, 0.25, 0.5 and 1.0 mg/kg. Animals were observed for clinical signs and food intake daily and were weighed regularly.

Hysterectomies were performed on day 28 post-insemination. All fetuses were weighed and examined for external and buccal anomalies and half of each litter were examined for visceral anomalies and the other half for skeletal anomalies and degree of ossification.

At the high dose level (1.0 mg/kg) there was an increase in the number of supernumerary ribs and delayed pubic ossification in the fetuses. The no observed effect level for maternal and fetotoxicity was 0.5 mg/kg/day.

Fetotoxicity in Rabbits Protocol Nos. 89004 and 89005 started 01/02/89

A second rabbit fetotoxicity study was conducted using a protocol identical to that summarized above but with dose levels of 1.0, 2.0 and 4.0 mg/kg/day.

At the high dose level two dams died and one was sacrificed as moribund. Body weight decreases in the high dose level were noted before, during and after treatment. The mean fetal weight at the high dose level was lower than controls. At 4 mg/ kg/day, the number of fetuses with supernumerary ribs was higher than other groups. A slight delay in ossification of pubic bones was observed at 4 mg/kg/day and 2 mg/kg/day. The no observed effect level for maternal and fetotoxicity was 1.0 mg/kg/day.

6. Genetic Toxicology

Semduramicin was evaluated in the following battery of in vivo and in vitro tests to assess its mutagenic potential.

Ames Test Protocol No. 85-564-02 started 12/17/85

Semduramicin was tested in vitro directly against Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100. No mutagenic activity was observed in the direct test for semduramicin at levels ranging from 0.02 to 10 mg/plate. Semduramicin was insoluble at levels of 0.5 mg/plate and above. All four strains were also used in metabolic activation assays with microsomal enzymes from Aroclor-1254 induced rat liver and semduramicin levels ranging from 0.002 to 1.0 mg/plate. No activation to a mutagenic metabolite was observed with any of these strains.

Mouse Lymphoma (L5178Y/TK Gene Mutation Assay) Protocol No. 85-564-02 started 10/28/85

Semduramicin at concentrations of 16 to 121 ug/ml was tested for in vitro mutagenic potential both with and without rat liver S9 activation. Cytotoxicity was observed at levels greater than 68 ug/ml.

Based on determination of total relative growth, mutant yield and mutant frequency, there was no indication of mutagenic activity either with or without metabolic activation.

Unscheduled DNA Synthesis Hazleton Protocol No. 12179-0-447R started 04/19/90

Semduramicin was tested for its ability to induce unscheduled DNA synthesis (UDS) in primary cultures of rat hepatocytes. UDS is considered indicative of DNA repair processes which occur following genetic damage. Levels of 0.0005 to 250 ug semduramicin/ml were tested while evidence of insolubility was observed at and above 100 ug/ml. Treatments from 2.5 ug/ml to 250 ug/ml were not analyzed for nuclear labeling due to high toxicity. The degree of DNA damage was determined by the amount of nuclear tritiated thymidine incorporation measured by autoradiography. Based on nuclear grain counts, semduramicin did not produce an elevation in UDS and was not damaging to DNA.

7. Special Toxicology Study

Cardiovascular Effects of Semduramicin Following Oral and Intravenous Administration in Conscious Dogs Battelle Protocol No. 874-R-8302 started 07/16/91

Six dogs were used to evaluate the cardiovascular effects of semduramicin. The test substance was administered in a single dose either intravenously (IV) at doses of 0.1, 0.3, and 0.6 mg/kg or orally at 0.3, 1.0, and 3.0 mg/kg.

Intravenous injection produced effects at all dose levels. Acute effects occurring 10 minutes of IV treatment included: (1) mild increase in average coronary flow and concomitant decreases in average vascular resistance at the 0.1 and 0.3 mg/kg dose, (2) dramatic increases in coronary flow and decreases in coronary

vascular resistance with the 0.6 mg/kg dose. Longer duration effects (~ 1 hour) after IV dosing included, (1) elevated heart rates after the 0.3 and 0.6 mg/kg doses, (2) mild increases in coronary flow and decreases in coronary vascular resistance after the 0.6 mg/kg dose, and (3) mild increases in total peripheral resistance after the 0.6 mg/kg dose.

After oral administration, no consistent dose related changes were detected in cardiovascular patterns and the no observed effect level was 3.0 mg/kg. Previous studies had established 4.0 mg/kg as the maximal tolerated dose for semduramicin producing ataxia.

This study was to conducted to determine a margin of safety between the two routes of administration. This study identified 3.0 mg/kg as the no observed effect level for oral dose and 0.1 mg/kg as an effect level for IV administration. A thirty fold margin of safety was established between oral and IV administrations.

B. Safe Concentration of Residues (Based Upon Threshold Assessment Guidelines)

The dog was the most sensitive laboratory animal species with a No-Observed-Effect Level of 0.3 mg semduramicin/kg/day in a one-year conventional toxicology evaluation. Applying a 100-fold safety factor, the Acceptable Daily Intake (ADI) and Safe Concentration (SC) of total residues, expressed as semduramicin free acid, are calculated as follows:

Acceptable Daily Intake (ADI):

ADI = NOEL X 60 kg / 100 = 0.3 mg/kg/day x 60 kg / 100 = 0.18 mg/day

Safe Concentration (SC): For Muscle

SC = ADI / 0.5kg = 0.18 mg / 0.5kg = 0.36 mg/kg = 360 ppb

On a molecular weight basis semduramicin, as the free acid, represents 97.5 % of semduramicin sodium. The SC in muscle tissue for total residues expressed as semduramicin sodium is 369 ppb.

Safe concentrations of residues for edible tissues other than muscle are based on "Consumption Factors" which adjust the SC's in proportion to the amount of tissue-type consumed on a daily basis:

TISSUE	CONSUMPTION FACTOR	SAFE CONCENTRATION
LIVER	3	1108 ppb
SKIN	2	738 ppb
FAT	2	738 ppb

C. Metabolism and Total Residue Depletion Studies

Protocol No. 1515N-60-87-005 Total Residue Depletion Study in Broiler Chickens

C14-semduramicin sodium was administered to 37 one day-old broiler chickens for seven days via feed containing 25 ppm semduramicin (free acid) activity. Following the period of medication, three chickens of each sex were sacrificed at 6, 12, 24 and 48 hours withdrawal.

Samples of liver, muscle, skin (with adhering fat) and fat (abdominal) were obtained from each animal and total residues quantitated by scintillation counting with a lower validated analytical sensitivity limit of 10 ppb. At all time points, some of the individual muscle samples were below the analytical limit and mean total residues expressed as semduramicin sodium never exceeded 15 ppb. For the other edible tissues, mean total residues were determined for each time point as follows:

Time (hr)	**Total Residues [ppb (1 SD)] - Liver**	**Total Residues [ppb (1 SD)] - Skin**	**Total Residues [ppb (1 SD)] - Fat**
6	273 (79)	57 (15)	74 (18)
12	112 (23)	22 (6)	27 (8)
24	58 (5)	15 (3)	15 (3)
48	31 (5)	11* (1)	11* (2)
120	18 (3)	9* (2)	10* (2)

* Some individual values below the validated lower limit of analytical quantitation of 10 ppb.

The liver samples from these birds were pooled for evaluation of degree of residue binding. At the 6 hour withdrawal point, 9% of the total residues were bound. This increased to 45% at 120 hours. Liver is the only edible tissue where appreciable levels of residues are found. As defined by HPLC, approximately 45% of the total residues in liver is unchanged semduramicin sodium at 6 hours withdrawal. There are other, more polar, metabolites, none of which exceed a concentration of 0.1 ppm or represent more than 10% of the total residues. Two of the low level metabolites have been identified as desmethyl derivatives and a third as a ring-opened product.

Unchanged semduramicin sodium and the more prominent minor metabolites have been detected in the livers of both the dog and rat following oral administration of semduramicin sodium. This confirms the exposure of the toxicology laboratory animal species to a metabolite profile consistent with that produced within the target species. These data demonstrate that total residues of semduramicin and its metabolites are well below the safe concentrations in all edible tissues at zero withdrawal time.

D. Regulatory Method of Analysis

The requirement for a regulatory method to monitor residues of semduramicin in chickens was waived. The waiver was granted because total residues of the drug were well below the safe concentrations in edible tissues of chickens that were dosed with 14C-semduramicin and sacrificed at a practical zero withdrawal (6 hours).

The regulatory limits of the assay (HPLC) for the Type A medicated article are 90 to 110%. The assay method to determine the concentration of semduramicin in Type C medicated chicken feed was successfully evaluated in an inter-laboratory study. The method is acceptable for the assay of medicated broiler chicken feed containing 25 ppm or 22.7 g/t semduramicin. The regulatory limits are 85 to 110% of labeled claim.

The validated regulatory analytical method is Method S 188, "Assay and Identity of Semduramicin in Feeds by Normal-Phase Liquid Chromatography with Post-Column Reaction." The regulatory method is on file in Dockets Management Branch (HFA-

305), Park Building, 12420 Parklawn Drive, Rockville, Maryland 20855. The method is attached to the FOI Summary.

V. AGENCY CONCLUSIONS

The data submitted in support of this original NADA 140-940 satisfy the requirements of section 512 of the Federal Food, Drug and Cosmetic Act (FFDCA). The data demonstrate that semduramicin sodium, when used at the proposed conditions, is safe and effective for the labeled indications. The approval provides for the use of semduramicin sodium at 25 ppm to prevent coccidiosis in broiler chickens caused by Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix, and E. mivati/mitis. Proper use by non-veterinarians can be expected because poultry producers routinely use medicated feed containing an animal drug for the prevention of coccidiosis in broiler chickens. Directions are clearly written and there is reasonable certainty that the conditions of use, including mixing directions, on the label can and will be followed by the producer. The agency has concluded that this product can be approved for over-the-counter use.

The data demonstrates that total residues of semduramicin sodium and its metabolites are well below the safe concentrations in all edible tissues at a practical zero withdrawal time (6 hours). Consequently, the requirement for a regulatory method to monitor residues of the drug was waived.

Under section 512(c)(2)(F)(i) of the FFDCA this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

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.