Approval Date: April 6, 2005

AMENDED
FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-226

AVIAX (Semduramicin sodium) plus STAFAC (Virginiamycin) plus ROXARSONE (Roxarsone)

"For the prevention of coccidiosis caused by *Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix,* and *E. mivati/E.mitis,* for the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens"

Sponsored by:

Phibro Animal Health
710 Rt. 46 East, suite 401
Fairfield, NJ 07004

1. GENERAL INFORMATION:

a. File Number:	NADA 141-226
b. Sponsor:	Phibro Animal Health 710 Rt. 46 East, suite 401 Fairfield, NJ 07004 Drug Labeler Code: 066104
c. Established Name:	Semduramicin sodium Virginiamycin Roxarsone
d. Proprietary Name:	AVIAX STAFAC ROXARSONE
e. Dosage Form:	Type A medicated article
f. How Supplied:	50 lb bags
g. How Dispensed	OTC
h. Amount of Active Ingredient	Semduramicin sodium: AVIAX 22.7 grams per lb Virginiamycin: STAFAC 5, 10, 20, 50, and 227 grams per lb Roxarsone: ROXARSONE 10, 20, and 50 percent
i. Route of Administration:	Oral, *via* feed
j. Species/Class:	Broiler chickens
k. Recommended Dosage:	Semduramicin sodium at 22.7 grams per ton plus virginiamycin at 20 grams per ton plus roxarsone at 22.7 to 45.4 grams per ton. Feed continuously as sole ration throughout growth period.
l. Pharmacological Category:	Semduramicin sodium: anticoccidial Virginiamycin: antimicrobial Roxarsone: growth promotant
m. Indications:	For the prevention of coccidiosis caused by *Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix, E. mivati/E. mitis,* for the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

2. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in **animal feed** have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the sponsor fails to demonstrate that:

- there is substantial evidence to demonstrate that any active ingredient/animal drug intended only for the same use as another active ingredient/animal drug in the combination makes a contribution to the labeled effectiveness.

- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population.

- where the combination contains more than one nontopical antibacterial active ingredient/animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness.

Semduramicin sodium, as provided by Phibro Animal Health, has previously been separately approved for use in broiler chicken feeds for the prevention of coccidiosis caused by *Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix, E. mivati/E. mitis* [21 CFR 558.555 (d)(1)(ii)]. Virginiamycin, as provided by Phibro Animal Health, has previously been separately approved for use in broiler chicken feeds for the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin [21 CFR 558.635 (d)(2)(iii)]. Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation [21 CFR 558.530 (d)(1)(i)]. Effectiveness for all three drugs, semduramicin sodium, virginiamycin, and roxarsone, when administered alone in accordance with their approved uses and conditions of use, is demonstrated in Phibro Animal Health's approved NADAs 140-940 and 091-467, and in Alpharma Inc.'s approved NADA 092-953, to which Phibro Animal Health has a right of reference, respectively.

Because semduramicin sodium, virginiamycin, and roxarsone each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that semduramicin sodium plus virginiamycin plus roxarsone provides appropriate concurrent use for the intended target population. The use of semduramicin sodium plus virginiamycin plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (semduramicin sodium, coccidiosis; virginiamycin, necrotic enteritis; roxarsone, growth performance) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (virginiamycin) contained in this combination animal drug intended for use in Type C medicated feed. Semduramicin sodium is not considered to be an antibacterial animal drug for use in broiler chickens for the purposes of §512(d)(4) of the FFDCA, because semduramicin sodium is approved only for prevention of a

protozoal disease in broiler chickens. Roxarsone is not considered to be an antibacterial animal drug for use in broiler, roaster, or replacement (breeder and layer) chickens for the purposes of §512(d)(4) of the FFDCA, because roxarsone is not approved for use in broiler, roaster, or replacement (breeder or layer) chickens for the diagnosis, cure, mitigation, treatment or prevention of bacterial disease and is not approved for any other use the Center for Veterinary Medicine deems attributable to its antibacterial properties.

3. TARGET ANIMAL SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and FDA finds that the application fails to show that the combination is safe, or

- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and FDA finds that the application fails to show that the combination is safe.

Semduramicin sodium, as provided by Phibro Animal Health, has previously been separately approved for use in broiler chicken feeds for the prevention of coccidiosis caused by *Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix, E. mivati/E. mitis* [21 CFR 558.555 (d)(1)(ii)]. Virginiamycin, as provided by Phibro Animal Health, has previously been separately approved for use in broiler chicken feeds for the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin [21 CFR 558.635 (d)(2)(iii)]. Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation [21 CFR 558.530 (d)(1)(i)].

Target animal safety for all three drugs, semduramicin sodium, virginiamycin, and roxarsone, when administered alone in accordance with their approved uses and conditions of use, is demonstrated in Phibro Animal Health's approved NADAs 140-940 and 091-467, and in Alpharma Inc.'s approved NADA 092-953, to which Phibro Animal Health has a right of reference, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of semduramicin sodium or virginiamycin or roxarsone when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Thus, pursuant to FFDCA, as amended by the ADAA of 1996, no specific target animal safety study(ies) are required for approval of NADA 141-226.

4. HUMAN SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human food safety grounds unless FDA finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or

- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity:

Safety for this combination has been established by data in NADA 140-940 (semduramicin sodium), NADA 091-467 (virgniamycin), and NADA 092-953 (roxarsone).

B. Tolerances for Residue:

Safety of semduramicin sodium, virginiamycin, and roxarsone have been established by NADAs 140-940, 091-467, and 092-953, respectively. Tolerances for residues of parent semduramicin sodium in uncooked edible tissues of chickens are established at 400 parts per billion (ppb) in liver and 130 ppb in muscle, in 21 CFR 556.597. No tolerance is required for virginiamycin (21 CFR 556.750). Tolerances for residues of arsenic from roxarsone in chickens are established at 0.5 ppm in uncooked muscle tissue, 2 ppm in uncooked edible by-products, and 0.5 ppm in eggs (21 CFR 556.60).

C. Residue Data:

A study entitled "Tissue Residue Non-Interference Study in Broiler Chickens Using Medicated Feed Containing Semduramicin Sodium, Roxarsone, and Virginiamycin," was conducted at Pfizer, Inc. Lee's Summit, MO and Hazelton Labs, Madison, WI under Pfizer experiment number 2511S-60-94-035, to establish that each drug in the presence of the others does not exceed its established tolerance, and that each drug does not interfere in the assay of the others. This study determined non-interference for two-way (semduramicin sodium and virginiamycin) and three-way (semduramicin sodium, virginiamycin, and roxarsone) drug combination use. Results for the two-way semduramicin sodium-virginiamycin combination are summarized in the FOI for NADA 141-114. Results for the three-way combination are reported here.

Broiler chickens were fed nonmedicated starter diet from Day 0 through Day 20. From Day 21 through 38, 100 birds (50 males, 50 females) were fed medicated feed containing 20 g/ton (22 ppm) ^{14}C-virginiamycin plus 22.7 g/ton (25 ppm) semduramicin sodium plus 45.4 g/ton (50 ppm) roxarsone. Fifty birds (25 males, 25 females) acted as control animals and were fed unmedicated feed thoroughout the test period. All birds were fed unmedicated feed from Day 38 to slaughter.

Six test birds (3 males, 3 females) were slaughtered at 0, 6, and 12 hours for semduramicin sodium and virginiamycin analyses, and at 0, 24, 72, and 120 hours for roxarsone analysis, and livers were collected for these analyses. The livers were analyzed by combustion for ^{14}C-virginiamycin, by an established HPLC method for semduramicin sodium, and an AOAC spectrophotometric method for roxarsone (arsenic). The results are presented in Table 1.

Table 1: Mean Virginiamycin, Semduramicin Sodium, and Roxarsone (arsenic) Residues in Liver Collected from Broiler Chickens Treated with Medicated Feed Containing 20 g/ton ^{14}C-virginiamycin, 22.7 g/ton semduramicin sodium, and 45.4 g/ton roxarsone

Withdrawal Time in Hours	Virginiamycin (ppb ± SD)		Semduramicin Sodium (ppb ± SD)		Roxarsone (ppm ± SD)	
	Male	Female	Male	Female	Male	Female
0	75 ± 17	76 ± 28	194 ± 38	162 ± 32	1.73 ± 0.58	1.62 ± 0.03
6	63 ± 10	68 ± 4	<40	98 ± 29	NA	NA
12	50 ± 46	64 ± 15	67 ± 36	<40	NA	NA
24	NA	NA	NA	NA	1.16 ±0.41	1.20 ± 0.10
72	NA	NA	NA	NA	0.70 ± 0.12	0.64 ± 0.06
120	NA	NA	NA	NA	0.38 ± 0.06	0.68 ± 0.28

NA = Not applicable.

Samples of control liver were fortified individually and in combination at levels of 0.4 ppm semduramicin sodium, 2 ppm arsenic, and 0.3 ppm ^{14}C-virginiamycin. The samples were then analyzed for semduramicin. The recovery ranged from 74.0 to 89.5% which was consistent with the validated method for semduramicin sodium in liver. It is concluded that there was no analytical interference for semduramicin sodium in liver due to the presence of other substances. Noninterference testing was not conducted for arsenic and virginiamycin because an ashing procedure and a combustion procedure were used for arsenic and virginiamycin, respectively.

Residues of virginiamycin and semduramicin sodium were below their respective tolerances at zero withdrawal, the established withdrawal period for these two drugs. Residues of roxarsone were also below tolerance at zero withdrawal (the established withdrawal time for roxarsone is 5 days).

The results of the study support the assignment of a 5-day withdrawal period for broiler chickens fed semduramicin sodium (22.7 g/ton), virginiamycin (20 g/ton), and roxarsone (22.7 to 45.4 g/ton) and demonstrate that there is no assay interference among the three drugs.

D. Regulatory Methods for Residues:

Regulatory analytical methods for semduramicin sodium and virginiamycin are not required. A spectrophotometric method is used to assay tissues for roxarsone residues. The method entitled "Arsenic (Total) Residues in Animal Tissues, Spectrophotometric Method" is published in the AOAC, 15th Edition 973.78, page 626.

E. User Safety Concerns:

There are no human warnings on the Type C Medicated Feed labeling.

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of Section 512(d)(4) of the FFDCA and 21 CFR Part 514 of the implementing regulations. The data demonstrate that this combination of semduramicin sodium (22.7 g/ton) plus virginiamycin (20 g/ton) plus roxarsone (22.7 to 45.4 g/ton) are safe and effective for the prevention of coccidiosis caused by *Eimeria tenella, E. acervulina, E. maxima, E. brunetti, E. necatrix, E. mivati/E. mitis,* for the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

Pursuant to 21 CFR 514.106(b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and effectiveness data in the parent NADAs.

The drugs are to be fed in Type C medicated feeds, in accordance with sections 2 and 3 of the FOI Summary and the Blue Bird labeling that is attached to this document.

Adequate directions for use have been written in labeling and there is reasonable certainty they will be followed in practice by poultry producers. Accordingly the agency has concluded that this combination use shall have over-the-counter marketing status.

The results of the study support the assignment of a 5-day withdrawal period for broiler chickens fed semduramicin sodium (22.7 g/ton), virginiamycin (20 g/ton), and roxarsone (22.7 to 45.4 g/ton) and demonstrate that there is no assay interference among the three drugs. Regulatory analytical methods for semduramicin sodium and virginiamycin are not required. A spectrophotometric method is used to assay tissues for roxarsone residues. The method entitled "Arsenic (Total) Residues in Animal Tissues, Spectrophotometric Method" is published in the AOAC, 15th Edition 973.78, page 626.

This approval does not qualify for marketing exclusivity under §512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Type C Broiler Chicken Medicated Feed Blue Bird Label

Net weight lb (kg) on bag or bulk

Semduramicin sodium + Virginiamycin + Roxarsone

Type C Broiler Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti, E. necatrix*, and *E. mivati/E. mitis*, for the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

ACTIVE DRUG INGREDIENTS

Semduramicin sodium	22.7 g/ton
Virginiamycin	20 g/ton
Roxarsone	22.7 to 45.4 g/ton

GUARANTEED ANALYSIS

Crude Protein, not less than	_____%
Lysine, not less than	_____%
Methionine, not less than	_____%
Crude Fat, not less than	_____%
Crude Fiber, not more than	_____%
Calcium, not less than	_____%
Calcium, not more than	_____%
Phosphorus, not less than	_____%
Salt[1], not less than	_____%
Salt[1], not more than	_____%
Sodium[2], not less than	_____%
Sodium[2], not more than	_____%

[1] If added.

[2] Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

INGREDIENTS

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

FEEDING DIRECTIONS

Feed continuously as the sole ration throughout growing period.

WARNING: Withdraw 5 days before slaughter.

CAUTION: Do not feed to laying chickens. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis. For broiler chickens only.

MANUFACTURED BY

BLUE BIRD FEED MILL

Any Town, USA 12345