*Approval Date:*_____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-150

Lasalocid (AVATEC®) plus Virginiamycin(STAFAC®)

For the prevention of coccidiosis caused by *Eimeria meleagrimitis,* *E. gallopavonis,* and *E. adenoeides*, and for increased rate of weight gain and improved feed efficiency in growing turkeys.

Sponsored by:

Roche Vitamins Inc.
45 Waterview Blvd.
Parsippany, New York 07054

FREEDOM OF INFORMATION SUMMARY

Combined use of AVATEC® and STAFAC® in Growing Turkey Feeds

I. GENERAL INFORMATION

NADA: 141-150

Sponsor: Roche Vitamins Inc.
45 Waterview Blvd.
Parsippany, NY 07054

Generic Names: Lasalocid
Virginiamycin

Trade Names: AVATEC®
STAFAC®

Marketing Status: OTC

II. INDICATIONS FOR USE

For the prevention of coccidiosis caused by *Eimeria meleagrimitis, E. gallopavonis,* and *E. adenoeides,* and for increased rate of weight gain and improved feed efficiency in growing turkeys.

III. DOSAGE

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles: lasalocid as per 21 CFR 558.311, and virginiamycin as per 21 CFR 558.635. Lasalocid is supplied as a Type A medicated article in a concentration of 90.7 grams lasalocid activity per pound. Virginiamycin is supplied as a Type A medicated article in concentrations of 20 and 227 grams of virginiamycin activity per pound.

B. Route of Administration: Oral, via the feed.

C. Recommended Dosage:

Lasalocid	Lasalocid is added to growing turkey feed at concentrations from 68 to 113 g/ton for the prevention of coccidiosis

	caused by *Eimeria meleagrimitis, E. gallopavonis,* and *E. adenoeides.*
Virginiamycin	Virginiamycin is added to growing turkey feed at concentrations from 10 to 20 g/ton for increased rate of weight gain and improved feed efficiency.

IV. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs 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 NADA fails to demonstrate that: 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) 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, or 3) where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness (21 USC 512 (d)(4)(D)).

Lasalocid, as provided by Roche Vitamins Inc., has previously been separately approved for use in growing turkeys for the prevention of coccidiosis caused by *Eimeria meleagrimitis, E. gallopavonis,* and *E. adenoeides* (21 CFR 558.311 (e)(1)(xiv)). Virginiamycin, as provided by Pfizer Inc., has previously been separately approved for use in growing turkey feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.635 (f)(2)(iv)). Effectiveness for each drug, lasalocid and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Roche Vitamins, Inc.'s last submitted drug experience report for lasalocid NADA 96-298, and in Pfizer Inc.'s previously approved NADA 91-467, to which Roche Vitamins Inc. has a right of reference. Because lasalocid and virginiamycin each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that lasalocid plus virginiamycin provide appropriate concurrent use for the intended target population. The use of lasalocid plus virginiamycin provides appropriate concurrent use because these drugs are intended to treat different conditions (lasalocid, coccidiosis; virginiamycin, performance) likely to occur simultaneously with sufficient frequency in growing turkeys. There is no more than one nontopical antibacterial (virginiamycin) contained in this combination animal drug intended for use in Type C medicated feed. Lasalocid is not considered to be an antibacterial animal drug for use in growing turkeys for the purposes of §512 (d)(4) of the FFDCA, because lasalocid is approved only for prevention of a protozoal disease in growing turkeys.

V. ANIMAL SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients 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 target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Lasalocid, as provided by Roche Vitamins Inc., has previously been separately approved for use in turkeys for the prevention of coccidiosis caused by prevention of coccidiosis caused by *Eimeria meleagrimitis, E. gallopavonis,* and *E. adenoeides* (21 CFR 558.311 (e)(1)(xiv)). Virginiamycin, as provided by Pfizer Inc., has previously been separately approved for use in turkey feed for increased rate of weight gain and improved feed efficiency (21 CFR 558.635 (f)(2)(iv)). Target animal safety for each drug, lasalocid and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Roche Vitamins Inc.'s approved NADA 96-298, and in Pfizer Inc.'s approved NADA 91-467, to which Roche Vitamins Inc. has a right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of lasalocid or virginiamycin 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 Animal Drug Availability Act of 1996, no specific target animal safety study (ies) is (are) required for approval of NADA 141-150.

VI. HUMAN SAFETY

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination 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 human safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity Tests

The toxicity studies that support the use of lasalocid and virginiamycin in turkeys are described in the FOI Summaries for the original NADAs that cover the use of these drugs in other food-producing species (lasalocid - NADA 96-298; virginiamycin - NADA 91-467).

B. Safe Concentrations and Tolerances

The toxicity studies referenced in Part A, above, were used to establish the safe concentrations in tissues of poultry listed below for lasalocid and virginiamycin.

	Safe Concentrations (ppm)		
	Muscle	Liver	Skin/Fat
lasalocid (NADA 96-298)	2.0	6.0	12.0
virginiamycin (NADA 91-467)	30.0	90.0	60.0

A tolerance of 400 ppb has been established under NADA 141-109 (combination approval for lasalocid and bacitracin zinc in turkeys) for residues of unchanged lasalocid in turkey liver. Tolerances for residues of virginiamycin in tissues of turkeys have not yet been established.

C. Residue Noninterference Study

A residue study was conducted in turkeys in order to demonstrate that the presence of each of the drugs in the two-way combination did not have an adverse effect on the tissue residue levels of the other drug. The study was conducted at Covance Laboratories, Inc., Madison, WI 53704 (Roche Study No. CD-97-24, Covance Study No. 6806-100).

At study initiation, 60 male and 60 female poults (breed BUTA) were selected for the study and were reared on unmedicated feed through Day 19 in two pens, one pen of males and one for females. From Day 19 onward, the turkeys were group housed in 12 pens. Initially there were 10 turkeys per pen, segregated by sex (i.e., six pens had 10 male turkeys each and six pens had 10 female turkeys each). On day 63, birds scheduled for testing were selected from the healthy birds in each group (by sex) using a computer generated random number assignment.

Five test diets, 1) unmedicated control, 2) lasalocid 113 g/ton + ^{14}C-virginiamycin 20 g/ton, 3) lasalocid 113 g/ton + virginiamycin 20 g/ton, 4) ^{14}C-virginiamycin 20 g/ton, or 5) lasalocid 113 g/ton, and were fed from day 63 to day 98. All the surviving birds on day 98 were sacrificed after a 6-hour drug withdrawal period, and livers were harvested for lasalocid and virginiamycin assays. The following results were observed:

		Mean Residue Levels (± SD) in Liver	
	Treatment	Lasalocid (ppm)	Virginiamycin (ppm)
Group 1	unmedicated controls	<0.005	<0.005
Group 2	Lasalocid + ^{14}C-virginiamycin	0.064 ± 0.055	0.088 ± 0.070
Group 3	lasalocid + virginiamycin	0.063 ± 0.049	<0.005
Group 4	^{14}C-virginiamycin	<0.005	0.024 ± 0.026
Group 5	Lasalocid	0.041 ± 0.020	<0.005

A statistical analysis of the lasalocid assay results summarized above demonstrated that residues of lasalocid were well below its tolerance of 0.4 ppm in turkey liver following the dosing scheme used in the study. Similarly, total residues of virginiamycin were well below the safe concentration of 90 ppm for that drug in turkey liver. The levels of both lasalocid and virginiamycin were higher when administered in combination, but higher levels were still well below the allowed levels. Thus, each of the two drugs, when administered in combination to turkeys does not have an adverse effect on residue levels of the other drug.

It was also observed in the residue study that the concentrations of both drugs were generally higher in the livers of female birds as compared to the level in livers of the male birds. The trend was due in part to the higher consumption of the medicated feed on a body weight basis by the female birds.

D. Assay Noninterference Study

The noninterference of residues of virginiamycin on the assay for parent lasalocid in turkey liver was demonstrated by the assay of control turkey liver spiked with lasalocid (25 ppb) with and without spiked virginiamycin (25 ppb and 100 ppb). Recoveries of lasalocid were in the range of 85% to 95% for each of the spiked liver samples, confirming noninterference on the assay. No assay noninterference work was required with virginiamycin, because residues of that drug in residue studies are determined by the use of ^{14}C-virginiamycin and the assay of tissues by radiochemical techniques.

E. Regulatory Methods

Official regulatory methods have not been adopted for lasalocid or for virginiamycin in edible tissues of turkeys. A research method based upon HPLC has been developed by Roche Vitamins for the assay of unchanged lasalocid in turkey liver (Roche SOP No. VFAASR220BML290).

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of § 512 of the FFDCA and demonstrate that lasalocid (68 to 113 g/ton) plus virginiamycin (10 to 20 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary.

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 efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with Section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

Residues of lasalocid were well below its tolerance of 0.4 ppm in turkey liver following the dosing scheme used in the submitted study. Similarly, total residues of virginiamycin were well below the safe concentration of 90 ppm for that drug in turkey liver. Tolerances for residues of virginiamycin in tissues of turkeys have not yet been established. Official regulatory methods have not been adopted for lasalocid or for virginiamycin in edible tissues of turkeys.

Attached labeling: Type C medicated feed (Blue Bird).