FREEDOM OF INFORMATION SUMMARY

Combined use of COBAN® and STAFAC® in Turkey Feeds

I. GENERAL INFORMATION:

NADA: 141-110

Sponsor: Elanco Animal Health
A Division of Eli Lilly and Company
2001 West Main Street
Greenfield, IN 46140

Generic Names: Monensin
Virginiamycin

Trade names: COBAN®
STAFAC®

Marketing status: OTC

II. INDICATIONS FOR USE:

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

III. DOSAGE:

A. Form: This NADA provided for the combined use of these two Type A medicated articles, monensin as per 21 CFR §558.355, and virginiamycin as per 21 CFR §558.635. Monensin is supplied as a Type A medicated article in a single concentration of 60 grams of monensin activity per pound. Virginiamycin is supplied as Type A medicated articles in concentrations of 20 and 227 grams of virginiamycin activity per pound.

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

C. Recommended Dosage:

Monensin	Monensin is added to growing turkey feed at concentrations from 54 to 90 g/ton for the prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis,* and *E. gallopavonis*.

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.

CAUTION: Do not allow horses, other equines, mature turkeys, or guinea fowl access to feed containing monensin. Ingestion of monensin by horses, mature turkeys, and guinea fowl has been fatal. Some strains of turkey coccidia may be monensin tolerant or resistant. Monensin may interfere with development of immunity to turkey coccidiosis.

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)).

Monensin, as provided by Elanco Animal Health, has previously been separately approved for use in feed for growing turkeys for the prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis,* and *E. gallopavonis* (21 CFR §558.355 (f)(2)(i). Virginiamycin, as provided by Pfizer Inc., has previously been separately approved for use in feed for growing turkeys for increased rate of weight gain and improved feed efficiency (21 CFR §558.635 (f)(2)(iv)). Effectiveness for each drug, monensin and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 130-736, and in approved NADA 91-467, to which Elanco Animal Health has a right of reference.

Because virginiamycin is intended for a different use than monensin, the NADA need not demonstrate, by substantial evidence, that virginiamycin contributes to the labeled effectiveness of the combination. Because monensin and virginiamycin each has at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that monensin plus virginiamycin provides appropriate concurrent use for the intended target population. The use of monensin plus virginiamycin provides appropriate concurrent use because these drugs are intended to treat different conditions (monensin,

coccidiosis; virginiamycin, improved performance) likely to occur simultaneously with sufficient frequency in growing turkeys. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed. Monensin 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 monensin is approved only for prevention of a protozoal disease in growing turkeys.

V. ANIMAL SAFETY:

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 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.

Monensin, as provided by Elanco Animal Health, has previously been separately approved for use in feed for growing turkeys for the prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis,* and *E. gallopavonis* (21 CFR §558.355 (f)(2)(i). Virginiamycin, as provided by Pfizer Inc., has previously been separately approved for use in feed for growing turkeys for increased rate of weight gain and improved feed efficiency (21 CFR §558.635 (f)(2)(iv)). Target animal safety for each drug, monensin and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Elanco Animal Health's approved NADA 130-736, and in approved NADA 91-467, to which Elanco Animal Health has a right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of monensin 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) are required for approval of NADA 141-110.

VI. HUMAN SAFETY:

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 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 Studies and Safe Concentrations of Residues

The basic safety data for monensin may be found in parent NADA 38-878 (COBAN® for Chickens) and for virginiamycin in NADA 91-467. Those data support the following safe concentrations for residues in tissues of turkeys as listed in 21 CFR 556.420 for monensin and in the FOI Summary for a Supplement to NADA 91-467 approved in 1988 for the use of virginiamycin in turkey feeds.

Monensin:	1.5 ppm	in muscle
	3.0 ppm	in skin with adhering fat
	4.5 ppm	in liver
Virginiamycin:	30 ppm	in muscle
	90 ppm	in liver
	60 ppm	in skin/fat

B. Residue and Assay Noninterference Studies

A tissue residue depletion study (No. AAC8806) was conducted at Lilly research Laboratories, a Division of Eli Lilly and Company, to demonstrate that there are no significant differences in the residue levels of monensin or virginiamycin at practical zero withdrawal when they are used alone and in combination. As part of that work and also with a storage stability study, assay noninterference studies were performed to confirm that residues of virginiamycin do not interfere with the assay for residues of monensin in tissues of turkeys. Because there is no cold analytical method for residues of virginiamycin, residues of that component of the combination were determined by the feeding of ^{14}C-virginiamycin and the radioassay of tissue samples to give the levels of virginiamycin total residues present.

Experiment No. AAC8806 was carried out using Nicholas white turkeys that were arranged in the treatment groups listed below. Drug treatments were started when the birds were 49 days of age.

Group Number	Birds per Group	Drug Treatment	Days on Treatment	Assay
1	4M + 4F	None	35	^{14}C-virginiamycin
2	4M + 4F	None	35	monensin
3	4M + 4F	^{14}C-Vm + Mon	35	^{14}C-virginiamycin
4	8M + 8F	Vm + Mon	35	monensin
5	4M + 4F	^{14}C-Vm	35	^{14}C-virginiamycin
6	4M + 4F	Mon	35	monensin

Vm = virginiamycin
Mon = monensin

At the end of the treatment period, all birds were sacrificed at a practical zero withdrawal (6 hours post treatment), and samples of skin/fat and liver were collected. The liver samples from the birds in Treatment Groups 3 and 5 were radioassayed to determine the levels of ^{14}C-virginiamycin total residues present. The skin/fat samples from the birds in Treatment Groups 4 and 6 were assayed using Elanco's bioautographic procedure for microbiologically active residues of monensin. A summary of the assay results is shown below.

Group	Treatment	Monensin (ppm) in skin/fat	Virginiamycin (ppm) in liver
3	^{14}C-Vm + Mon		0.102
4	Vm + Mon	<0.04-0.063	
5	^{14}C-Vm		0.095
6	Mon	<0.04	

Vm = virginiamycin
Mon = monensin

The tissue residue assay results shown above demonstrate that there are no significant differences in the residue levels of monensin or virginiamycin at practical zero withdrawal when the drugs are used alone or in combination. Similarly, the assay noninterference work done along with Study AAC8806 and in a residue storage stability study demonstrate that the

presence of residues of virginiamycin does not affect the bioassay for residues of monensin in turkey skin/fat.

VII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that monensin (54 to 90 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.

Residue assay results demonstrate that there are no significant differences in the residue levels of monensin or virginiamycin at practical zero withdrawal when the drugs are used alone or in combination.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for food producing animals does not qualify for marketing exclusivity because the application does not contain substantial evidence of the effectiveness of the drugs involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant.

Attached labeling: Type C medicated Feed (Blue Bird)