Approval Date: June 28 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 140-955

Monensin (COBAN®) plus Bambermycins (FLAVOMYCIN®)

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.

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

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

FREEDOM OF INFORMATION SUMMARY

Combined use of COBAN® and FLAVOMYCIN® in Growing Turkey Feeds

I. GENERAL INFORMATION

NADA: 140-955

Sponsor: Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Generic Names: Monensin
Bambermycins

Trade Names: COBAN®
FLAVOMYCIN®

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.

For the prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis,* and *E. gallopavonis,* and for 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: monensin as per 21 CFR 558.355, and bambermycins as per 21 CFR 558.95. Monensin is supplied as a Type A medicated article in a concentration of 45 or 60 grams monensin activity per pound. Bambermycins is supplied as a Type A medicated article in concentrations of 2, 4, or 10 grams of bambermycins activity per pound.

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

C. Recommended Dosage:

Monensin	Monensin is added to growing turkey feed at a concentrations from 54 to 90 g/ton for the prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis,* and *E. gallopavonis.*
Bambermycins	Bambermycins is added to growing turkey feed at concentrations from 1 to 2 g/ton for improved feed efficiency, and at a concentration of 2 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)).

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)). Bambermycins, as provided by Hoechst Roussel Vet, has previously been separately approved for use in feed for growing turkeys for improved feed efficiency and for increased rate of weight gain and feed efficiency (21 CFR 558.95(d)(3)(i) and (d)(3)(ii) respectively). Effectiveness for each drug, monensin and

bambermycins, 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 Hoechst-Roussel Vet's previously approved NADA 44-759, to which Elanco Animal Health has a right of reference. Because monensin and bambermycins each have at least one use that is different from the other when used in the proposed combination, the NADA must also demonstrate that monensin plus bambermycins provide appropriate concurrent use for the intended target population. The use of monensin plus bambermycins provides appropriate concurrent use because these drugs are intended to treat different conditions (monensin, coccidiosis; bambermycins, performance) likely to occur simultaneously with sufficient frequency in growing turkeys. There is no more than one nontopical antibacterial (bambermycins) 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 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.

Monensin, as provided by Elanco Animal Health, has previously been separately approved for use in growing turkey feed for the prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis,* and *E. gallopavonis* (21 CFR 558.355(f)(2)(i)). Bambermycins, as provided by Hoechst Roussel Vet, has previously been separately approved for use in growing turkey feed for improved feed efficiency and for increased rate of weight gain and improved feed efficiency (21 CFR 558.95(d)(3)(i) and (d)(3)(ii) respectively). Target animal safety for each drug, monensin and bambermycins, 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 Hoechst-Roussel Vet's approved NADA 44-759, 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 bambermycins 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 studies are required for approval of NADA 140-955.

VI. HUMAN SAFETY

A. Toxicity Tests and Safe Concentrations of Residues

The basic safety data for monensin may be found in the parent NADA 38-878 (COBAN® for chickens) and for bambermycins in NADA 44-759. Those data support the following safe concentrations for residues in tissues of turkeys as listed in 21 CFR 556.420 for monensin. Listing safe concentrations and tolerances for bambermycins are not required.

Monensin:	1.5 ppm in muscle
	3.0 ppm in skin with adhering fat
	4.5 ppm in liver

B. Residue and Assay Noninterference Studies

A tissue residue study was conducted to demonstrate there is no change in the residue depletion pattern for monensin when both drugs (bambermycins and monensin) were fed to turkeys. There were two segments to the study: (1) validation of the assay by assaying spiked tissue samples with the cited drugs, and (2) assays for monensin conducted on tissue samples harvested from medicated birds raised in commercial production. Four male and four female turkeys medicated with monensin (90 g/ton) and bambermycins (4 g/ton) for 12 weeks were slaughtered at zero day withdrawal (6 hr.). The tissues were assayed for monensin (skin/fat). All tissues tested showed less than 0.04 ppm monensin which is the limit of detection for the assay. These results are comparable to those obtained when monensin is administered alone and confirm the noninterference of bambermycins on the depletion of monensin. Tissue assay noninterference and method validation studies for monensin tissue assay were conducted by spiking control samples with bambermycins and monensin and then assaying for monensin residues. The assay results demonstrated that there is no interference by bambermycins on the monensin tissue assay.

Substantial scientific information provided by Hoechst Roussel Vet shows that the likelihood of other drugs in combination with bambermycins altering the bambermycins residues in tissues of animals is extremely improbable; there are no longer requirements for conducting studies demonstrating tissue residue and analytical method non-interference for Hoechst Roussel Vet's bambermycins where it is included at already approved levels. Such is the case for this combination. Data generated over many years shows that residues of bambermycins are not detected, whether the drug is used alone or in combination.

The available residue chemistry information supports the assignment of a zero day withdrawal period for growing turkeys fed the combination of monensin (54 to 90 g/ton) and bambermycins (1 to 2 g/ton).

VII. AGENCY CONCLUSIONS

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.

The data submitted in support of this NADA comply with the requirements of § 512 of the FFDCA and demonstrate that monensin (54 to 90 g/ton) plus bambermycins (1 to 2 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.

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

Net weight lb (kg) on bag or bulk

Monensin/Bambermycins Growing Turkey Ration

Type C Medicated Feed

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.

ACTIVE DRUG INGREDIENT

Monensin…….....……54 to 90 g/ton
Bambermycins…….....……..2 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.

DIRECTIONS FOR USE

Feed continuously as the sole ration.

CAUTION: Do not allow horses, other equines, mature turkeys, or guinea fowl access to feed containing monensin. Ingestion of monensin by horses 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.

MANUFACTURED BY
BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Monensin/Bambermycins Growing Turkey Ration

Type C Medicated Feed

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

ACTIVE DRUG INGREDIENT

Monensin…….....……54 to 90 g/ton
Bambermycins…….....……1 to 2 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…….....……_____%

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

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MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345