Approval Date: July 3, 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-164

Monensin (COBAN®) plus Tylosin phosphate (TYLAN®)

As an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

Sponsored by:

Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

FREEDOM OF INFORMATION SUMMARY

Combined use of COBAN® and TYLAN® in Broiler Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-164

Sponsor: Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

Generic Names: Monensin
Tylosin phosphate

Trade Names: COBAN®
TYLAN®

Marketing Status: OTC

II. INDICATIONS FOR USE:

As an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

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(f)(1(i), and tylosin phosphate as per 21 CFR 558.625(f)(1)(iii). Monensin is supplied as a Type A medicated article in concentrations of 44, 45, or 60 grams monensin activity per pound. Tylosin phosphate is supplied as a Type A medicated article in concentrations of 10 grams of tylosin phosphate activity per pound.

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

C. Recommended Dosage:

Monensin	Monensin is added to broiler chicken feed at concentrations from 90 to 110 g/ton as an aid

	in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*.
Tylosin phosphate	Tylosin phosphate is added to chicken feed at concentrations from 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency.

CAUTION: Do not feed to laying chickens. Do not feed to chickens over 16 weeks of age. 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. Feed continuously as sole ration. In the absence of coccidiosis, the use of monensin with no withdrawal period may limit feed intake resulting in reduced weight gain.

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 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 NADA fails to demonstrate that 1) there is substantial evidence to indicate 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/animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Monensin, as provided by Elanco Animal Health, has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati*, and *E. maxima* (21 CFR 558.355(f)(1)(i)). Tylosin phosphate, as provided by Elanco Animal Health, has previously been separately approved for increased rate of weight gain and improved feed efficiency in chickens (21 CFR 558.625(f)(l)(iii)). Effectiveness for each drug, monensin and tylosin phosphate, when administered alone in accordance with its approved uses and conditions of

use, is demonstrated in Elanco Animal Health's approved NADAs 38-878 and 12-491, respectively.

Because monensin and tylosin phosphate each have at least one use that is different from the other animal drug used in the combination, the NADA must also demonstrate that monensin plus tylosin phosphate provide appropriate concurrent use for the intended target population. The use of monensin plus tylosin phosphate provides appropriate concurrent use because these drugs are intended to treat different conditions (monensin, coccidiosis; tylosin phosphate, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. Monensin is not considered to be an antibacterial animal drug for such use in broiler chickens for the purposes of Section 512(d)(4) of the FFDCA, because monensin is approved only for prevention of a protozoal disease (coccidiosis) in broiler chickens.

V. ANIMAL 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 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 a 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 broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati*, and *E. maxima* (21 CFR 558.355(f)(1)(i)). Tylosin phosphate, as provided by Elanco Animal Health, has previously been separately approved for increased rate of weight gain and improved feed efficiency in chickens (21 CFR 558.62(f)(l)(iii)). Target animal safety for each drug, monensin and tylosin phosphate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 38-878 and 12-491, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of monensin or tylosin phosphate 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 141-164.

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 Studies

Safety of this combination product has been established by data in NADA 95-735 and NADA 38-878 for monensin and NADA 12-491 for tylosin phosphate.

B. Tolerances

A tolerance for marker residues of monensin in chickens is not needed. For tylosin phosphate, a tolerance of 0.2 ppm (negligible residue) in uncooked fat, muscle, liver, and kidney in chickens has been previously codified under 21 CFR 556.740.

C. Residue Non-interference Study

Residue data supporting the approved uses of monensin and tylosin phosphate, each having zero withdrawal times, were submitted to their respective original applications (see Part A, above). The following study (Study No. T1X909703) was conducted at Elanco Animal Health, Greenfield, IN to establish that the depletion of each drug in the presence of the other is not affected and that the presence of the drugs in the same broiler tissue did not interfere with the assay of the drugs. In addition to providing data for the two-way combination product, the results of this study were used to support the three-way combination product, monensin plus tylosin phosphate plus roxarsone, in broiler chickens.

Hubbard/White Cross (Cornish Cross) broiler chickens (70 males and 70 females), approximately 3 weeks of age, were allocated to one control group and five treatment groups (with one serving as a replacement group). Test birds were allowed *ad libitum* access to medicated feed with 110 g/ton monensin, 50 g/ton tylosin phosphate, and 45.4 g/ton roxarsone for three weeks. Control birds were fed unmedicated basal ration *ad libitum*. Test birds were euthanized at zero (6 hours), 24, 72, and 120 hours

withdrawal. Control birds were euthanized at zero withdrawal. Liver and skin with adhering fat were collected from each bird as appropriate for residue assay. The official microbiological methods were used to detect monensin residues in the skin/fat and tylosin phosphate in the liver. Arsenic residues in livers were determined by a validated version of the regulatory AOAC method.

Monensin residues in skin/fat were not detectable (i.e., < 0.05 ppm) at zero withdrawal. Residues of tylosin phosphate in liver were below the tolerance level at zero withdrawal. These data indicate the absence of interference in the depletion pattern of the individual drugs. Therefore, the data support assignment of a zero withdrawal time for the two-way combination, monensin plus tylosin phosphate.

Samples of control skin/fat and control liver were fortified with monensin, tylosin phosphate, and roxarsone. The data showed that the presence of tylosin phosphate and roxarsone did not interfere with the assay of monensin, and that the presence of roxarsone and monensin did not interfere with the assay of tylosin phosphate. A non-interference study for roxarsone was not necessary because the assay method for roxarsone is done by ashing the tissue prior to determination of the roxarsone residues.

D. Regulatory Methods for Residues

The regulatory analytical method for monensin is the method developed by Eli Lilly and Company, P. O. Box 708, Greenfield, Indiana 46140 (Method 5801654, "Determination of Monensin in Tissues and Eggs"). The regulatory method for detection of residues of tylosin phosphate is a microbiological test using *Micrococcus luteus* (ATCC 9341) as the test organism. These methods are on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

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 (90 to 110 g/ton) plus tylosin phosphate (4 to 50 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) - Broiler chickens

Net weight lb (kg) on bag or bulk

Monensin/Tylosin phosphate Broiler Chicken Ration

Type C Medicated Feed

As an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, and for increased rate of weight gain and improved feed efficiency in broiler chickens.

Active Drug Ingredient

Monensin……..……..90 to 110 g/ton
Tylosin phosphate…….……4 to 50 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 specifically named in accordance with the names and definitions adopted by the Association of American Feed Control Official's Publication.

Directions for Use

Feed continuously as sole ration.

(OVER)

CAUTION: Do not feed to laying chickens. Do not feed to chickens over 16 weeks of age. 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. Feed continuously as sole ration. In the absence of coccidiosis, the use of monensin with no withdrawal period may limit feed intake resulting in reduced weight gain.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345