Approval Date: June 28 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-139

Monensin (COBAN®) plus Roxarsone (3-NITRO®)

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, improved feed efficiency, and improved pigmentation in replacement chickens intended for use as cage layers.

Sponsored by:

Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

FREEDOM OF INFORMATION SUMMARY

Combined use of COBAN® and 3-NITRO® in Replacement Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-139

Sponsor: Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

Generic Names: Monensin
Roxarsone

Trade Names: COBAN®
3-NITRO®

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, improved feed efficiency, and improved pigmentation in replacement chickens intended for use as cage layers.

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)(4)(i), and roxarsone as per 21 CFR 558.530(d)(1)(i). Monensin is supplied as a Type A medicated article in concentrations of 45 or 60 grams monensin activity per pound. Roxarsone is supplied as a Type A medicated article in concentrations of 45.4, 90, 227 or 360 grams of roxarsone activity per pound.

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

C. Recommended Dosage:

Monensin	Monensin is added to replacement 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*.
Roxarsone	Roxarsone is added to growing chicken feed at concentrations from 22.7 to 45.4 g/ton for increased rate of weight gain, improved feed efficiency, and improved pigmentation.

WARNING: Withdraw 5 days before slaughter.

CAUTION: For replacement chickens intended for use as cage layers only. 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. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water may result in leg weakness or paralysis.

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 replacement chickens intended for use as cage layers 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)(4)(i)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for increased rate of weight gain, improved feed efficiency, and improved pigmentation in growing chickens (21 CFR 558.530(d)(l)). Effectiveness for each drug, monensin and roxarsone, when administered alone in accordance

with its approved uses and conditions of use, is demonstrated in approved NADAs 38-878 (to which Alpharma Inc. has a right of reference) and 7-891, respectively.

Because monensin 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 monensin plus roxarsone provide appropriate concurrent use for the intended target population. The use of monensin plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (monensin, coccidiosis; roxarsone, pigmentation problems) likely to occur simultaneously with sufficient frequency in replacement chickens intended for use as cage layers. Monensin is not considered to be an antibacterial animal drug for such use in 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 replacement chickens. Roxarsone is not considered to be an antibacterial animal drug for such use in replacement chickens for the purposes of Section 512(d)(4) of the FFDCA, because roxarsone is not approved for use in 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.

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 replacement chickens intended for use as cage layers 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)(4)(i)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for increased rate of weight gain, improved feed efficiency, and improved pigmentation in growing chickens (21 CFR 558.530(d)(l)). Target animal safety for each drug, monensin and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 38-878 (to which Alpharma Inc. has a right of reference) and 7-891, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of monensin 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 Animal Drug Availability Act of 1996, no specific target animal safety studies are required for approval of NADA 141-139.

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. Tolerances

Data establishing the safety of monensin and roxarsone have been established by NADAs 38-878 and 7-891, respectively. A tolerance for marker residues of monensin in chickens is not needed. 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).

B. Residue Data

A tissue residue study in chickens fed monensin (110 g/ton) and roxarsone (45.4 g/ton) was conducted. Muscle, liver, fat, and kidney tissues were collected at zero and 120 hour withdrawal times for determination of arsenic content and zero, 24, and 48 hour withdrawal times for determination of monensin residues. The arsenic levels of muscle (<0.2 ppm), liver (ranged from 0.24 to 0.62 ppm), fat (<0.2 ppm), and kidney (ranged form 0.2 to 0.23 ppm) at 120 hour withdrawal (5 days) were below the established tolerances. The sensitivity of the method for the determination of roxarsone as arsenic is at least 0.2 ppm. No residues of monensin were detected in muscle (lean) tissues at zero time withdrawal. At 24 hour withdrawal time no determinable residues of monensin were found in liver, fat, or kidney tissues. The assay method for monensin claimed a sensitivity of 0.025 to 0.05 mcg/gm. Thus, monensin residues in skin/fat were below the one-time tolerance of 0.05 ppm as early as 24 hours of withdrawal.

The available residue chemistry information supports the assignment of a five day withdrawal period for replacement chickens fed the combination of monensin (90 to 110 g/ton) and roxarsone (22.7 to 45.4 g/ton).

C. Regulatory Methods for Residues

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.

The regulatory analytical method for monensin is the method developed by Eli Lilly and Company, Box 708, Greenfield, IN 46140 (Method 5801654, Determination of Monensin in Tissues and Eggs") on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, MD 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 roxarsone (22.7 to 45.4 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), 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) - Replacement chickens intended for use as cage layers.

Net weight lb (kg) on bag or bulk

Monensin/Roxarsone Replacement 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, improved feed efficiency, and improved pigmentation in replacement chickens intended for use as cage layers.

Active Drug Ingredient

Monensin……..……..90 to 110 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 specifically named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

Directions for Use

Feed continuously as sole ration.

(OVER)

WARNING: Withdraw 5 days before slaughter.

CAUTION: For replacement chickens intended for use as cage layers only. 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. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345