Approval Date: June 28 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-138

Monensin (COBAN®) plus Bacitracin Methylene Disalicylate (BMD®) plus Roxarsone (3-NITRO®)

1. As an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in replacement chickens intended for use as cage layers.

2. As an aid in the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, 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®, BMD®, and 3-NITRO® in Replacement Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-138

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

Generic Names: Monensin
Bacitracin methylene disalicylate
Roxarsone

Trade Names: COBAN®
BMD®
3-NITRO®

Marketing Status: OTC

II. INDICATIONS FOR USE:

1) As an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*, as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in replacement chickens intended for use as cage layers;

2) As an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*, as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, 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 three Type A medicated articles, monensin as per 21 CFR 558.355(f)(4)(i), bacitracin methylene disalicylate as per 21 CFR 558.76(d)(1)(vi) and (ix), 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. Bacitracin

methylene disalicylate is supplied as a Type A medicated article in concentrations of 10, 25, 30, 50, 60, or 75 grams bacitracin 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*.
Bacitracin methylene disalicylate	1) Bacitracin methylene disalicylate is added to replacement chicken feed at a concentration of 50 g/ton as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin; 2) Bacitracin methylene disalicylate is added to replacement chicken feed at concentrations from 100 to 200 g/ton as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin.
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)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved as an aid in the prevention and control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in broiler chickens (21 CFR 558.76(d)(1)(vi) and (d)(1)(ix)). 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, bacitracin methylene disalicylate, 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) 46-592, and 7-891, respectively.

Because monensin, bacitracin methylene disalicylate, 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 bacitracin methylene disalicylate plus roxarsone provide appropriate concurrent use for the intended target population. The use of monensin plus bacitracin methylene disalicylate plus roxarsone provide appropriate concurrent use because these drugs are intended to treat different conditions (monensin, coccidiosis; bacitracin methylene disalicylate, necrotic enteritis; roxarsone, pigmentation problems) likely to occur simultaneously with sufficient frequency in replacement chickens intended for use as cage layers. There is no more than one nontopical antibacterial (bacitracin methylene disalicylate) 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 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)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved as an aid in the prevention and control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in broiler chickens (21 CFR 558.76(d)(1)(vi) and (d)(1)(ix)). 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, bacitracin methylene disalicylate, 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) 46-592, and 7-891, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of monensin, bacitracin methylene disalicylate, 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 study(ies) is (are) required for approval of NADA 141-138.

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, bacitracin methylene disalicylate, and roxarsone have been established by NADA 38-878, 46-592, and 7-891, respectively. A tolerance for marker residues of monensin in chickens is not needed. Tolerances for residues of bacitracin in uncooked edible tissues of chickens are established at 0.5 ppm (0.02 unit/g) in 21 CFR 556.70. 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

Male and female broiler chickens were fed medicated feed containing monensin at 110 g/ton, bacitracin methylene disalicylate at 50 g/ton, and roxarsone at 45.4 g/ton. Samples of muscle, liver, kidney, skin and fat were collected for drug residue assay at 0, 3, 5, and 6 days post withdrawal. The results show no microbiologically active bacitracin residue in any of the tissues at zero withdrawal time. The monensin data in tissues showed no detectable residues (i.e., <0.05 ppm) by 3 days of withdrawal. Thus, monensin residues in skin/fat were below the one time tolerance of 0.05 ppm well before the 5 day withdrawal period proposed for this combination. Roxarsone has a five day withdrawal period required. At five days post withdrawal, roxarsone residues in muscle, skin and fat were well below 0.5 ppm and the residues in liver and kidney were well below the 2 ppm tolerance for roxarsone. Additional information on residues for the combination of monensin, bacitracin methylene disalicylate, and roxarsone can be found in the Freedom of Information summary for NADA 116-088.

Non-interference among the active ingredients (monensin, bacitracin methylene disalicylate, and roxarsone) in tissue residue depletion at the longest withdrawal time (5 days) or in the performance of the analytical methods for tissue residues was demonstrated.
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), bacitracin methylene disalicylate (50 g/ton), and roxarsone (22.7-45.4 g/ton).

C. Tissue Residue Depletion Studies and Assay Non-interference

The residue data supporting the approved individual uses of monensin, bacitracin methylene disalicylate, and roxarsone, and their respective withdrawal times of 0, 0, 5 days have been submitted in their respective original applications.

Non-interference among the active ingredients (monensin at 110 g/ton, bacitracin methylene disalicylate at 50 g/ton, and roxarsone at 45.4 g/ton) when fed in a tissue residue depletion study demonstrated that the withdrawal times for the individual compounds were not altered. Additionally, the lack of interference in the performance of the analytical methods for tissue residues of the individual drugs was demonstrated in the original approval of this combination (NADA 116-088). Residue data submitted to the sponsor's approved application for a bacitracin zinc product (NADA 138-703) support the approval of this supplemental application for the combination use of 100 to 200 g/ton bacitracin methylene disalicylate, 90 to 110 g/ton monensin, and either 22.7 to 45.4 roxarsone in replacement chickens. The 5-day withdrawal period for this combination was confirmed in Study AEF-1-83, conducted by Thomas Kennedy, AEF Research, Waunakee, Wisconsin. An equal number of male and female broiler chickens were fed a diet containing 200 g/ton bacitracin zinc, 110 g/ton monensin, and 45 g/ton roxarsone for 48 days. The data showed that each drug depleted to its tolerance before the proposed 5 day withdrawal period. With respect to monensin, residues in skin/fat were less than the one-time tolerance of 0.05 ppm by 2 days of withdrawal.

D. Analytical Methods for Residues (Regulatory Methods)

The method for monensin is "Determination of Monensin in Tissues and Eggs," Method 5801654, Eli Lilly and Company, Box 708, Greenfield, IN 46140.

A microbiological method is used to assay tissues for bacitracin residues. The method entitled "Modified Microbiological Method for Determination of Bacitracin in Tissues" is on display in the Food and Drug Administration's Freedom of Information Publication Room (Room 1061), 5630 Fisher's Lane, Rockville, MD 20852.

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.

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 bacitracin methylene disalicylate (50 g/ton and 100 to 200 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)(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) - Replacement chickens intended for use as cage layers.

Net weight lb (kg) on bag or bulk

Monensin/Bacitracin Methylene Disalicylate/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*, as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, 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
Bacitracin methylene disalicylate ……..……50 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.

WARNING: Withdraw 5 days before slaughter.

(OVER)

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

Net weight lb (kg) on bag or bulk

Monensin/Bacitracin Methylene Disalicylate/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*, as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, 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
Bacitracin methylene disalicylate ……..……100 to 200 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

To control a necrotic enteritis outbreak, start medication at first clinical signs of disease. The dosage range permitted provides for different levels based on severity of the infection. Administer continuously for 5 to 7 days or as long as clinical signs persist, then reduce bacitracin methylene disalicylate to prevention level (50 g/ton).

(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