Approval Date: December 23, 1999

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-121

Salinomycin (BIO-COX®) plus Bacitracin methylene disalicylate (BMD®) plus Roxarsone (3-NITRO®)

I. **For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 broiler, roaster, and replacement (breeder and layer) chickens;**

II. **For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 broiler, roaster, and replacement (breeder and layer) chickens.**

Sponsored by:

Alpharma Inc.
One Executive Way
Fort Lee, NJ 07024

FREEDOM OF INFORMATION SUMMARY

Combined use of BIO-COX®, BMD®, and 3-NITRO®
in Broiler, Roaster, and Replacement (Breeder and Layer) Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-121

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

Generic Names: Salinomycin
Bacitracin methylene disalicylate
Roxarsone

Trade Names: BIO-COX®
BMD®
3-NITRO®

Marketing Status: OTC

II. INDICATIONS FOR USE:

1) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 broiler, roaster, and replacement (breeder and layer) chickens;

2) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 broiler, roaster, and replacement (breeder and layer) chickens.

III. DOSAGE:

A. Dosage form: This original NADA provides for the combined use of these three Type A medicated articles, salinomycin as per 21 CFR 558.550, bacitracin methylene disalicylate as per 21 CFR 558.76, and roxarsone as per 21 CFR 558.530. Salinomycin is supplied as a Type A medicated article containing 30 or 60 grams salinomycin activity per pound. Bacitracin methylene disalicylate is supplied as a Type A medicated article in concentrations

of 10, 25, 30, 40, 50, 60, or 75 grams bacitracin methylene disalicylate activity per pound. Roxarsone is supplied as a Type A medicated article in a concentrations of 45.4, 90, or 227 grams of roxarsone activity per pound.

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

C. Recommended Dosage:

Salinomycin	Salinomycin is added to broiler, roaster and replacement (breeder and layer) chicken feeds at concentrations from 40 to 60 g/ton for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati.*
Bacitracin methylene disalicylate	1) Bacitracin methylene disalicylate is added to broiler and replacement chicken feeds 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 broiler and replacement chicken feeds 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 feeds at concentrations from 22.7 to 45.4 g/ton for increased rate of weight gain, improved feed efficiency, and improved pigmentation.

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)).

Salinomycin, as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler, roaster, and replacement (breeder and layer) chicken feeds for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* (21 CFR 558.550 (d)(1)(i) and (d)(3)(i)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for use in broiler and replacement chicken feeds as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(vi)), and as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(ix)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530 (d)(1)(i)). Effectiveness for all three drugs, salinomycin, bacitracin methylene disalicylate, and roxarsone, when administered alone in accordance with their approved uses and conditions of use, is demonstrated in Roche Vitamins Inc.'s approved NADA 128-686, to which Alpharma Inc. has a right of reference, and in Alpharma Inc.'s approved NADAs 46-592 and 7-891, respectively.

Because salinomycin, 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 salinomycin plus bacitracin methylene disalicylate plus roxarsone provides appropriate concurrent use for the intended target population. The use of salinomycin plus bacitracin methylene disalicylate plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (salinomycin, coccidiosis; bacitracin methylene disalicylate, necrotic enteritis; roxarsone, growth performance) likely to occur simultaneously with sufficient frequency in broiler, roaster, and replacement (breeder and layer) chickens. 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. Salinomycin is not considered to be an antibacterial animal drug for use in broiler, roaster, and replacement (breeder and layer) chickens for the purposes of §512(d)(4) of the FFDCA, because salinomycin is approved only for prevention of a protozoal disease in broiler, roaster, and replacement (breeder and layer) chickens. Roxarsone is not considered to be an antibacterial animal drug for use in broiler, roaster, or replacement (breeder and layer) chickens for the purposes of §512(d)(4) of the FFDCA, because roxarsone is not approved for use in broiler, roaster, or replacement (breeder or

layer) 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 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.

Salinomycin, as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler, roaster, and replacement (breeder and layer) chicken feeds for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati* (21 CFR 558.550 (d)(1)(i) and (d)(3)(i)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for use in broiler and replacement chicken feeds as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(vi)), and as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR 558.76 (d)(1)(ix)). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in growing chicken feed for increased rate of weight gain, improved feed efficiency, and improved pigmentation (21 CFR 558.530 (d)(1)(i)). Target animal safety for all three drugs, salinomycin, bacitracin methylene disalicylate, and roxarsone, when administered alone in accordance with their approved uses and conditions of use, is demonstrated in Roche Vitamins Inc.'s approved NADA 128-686, to which Alpharma Inc. has a right of reference, and in Alpharma Inc.'s approved NADAs 46-592 and 7-891, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of salinomycin or 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) are required for approval of NADA 141-121.

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. Tolerances

Safety of bacitracin methylene disalicylate, salinomycin, and roxarsone have been established by NADAs 46-592, 128-686, and 7-891, respectively. 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. No tolerance is required for salinomycin. 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

The study entitled "Tissue levels in chickens fed salinomycin plus roxarsone plus bacitracin MD or salinomycin plus roxarsone plus zinc bacitracin," conducted under protocol BRMS 82-34 by A. H. Robins, Ashland, VA, is summarized thoroughly in the July, 1984, FOI Summary under NADA 135-321. The results of the study support the assignment of a 5-day withdrawal period for broiler chickens fed salinomycin (40 to 60 g/ton), bacitracin methylene disalicylate (50, or 100 to 200 g/ton), and roxarsone (22.7 to 45.4 g/ton) and demonstrate that there is no assay interference among the three drugs.

C. Regulatory Methods for Residues

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, 5600 Fisher's Lane, Rockville, MD 20857.

A regulatory analytical method for salinomycin is not required.

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 salinomycin (40 to 60 g/ton) plus bacitracin methylene disalicylate (50, or 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 Sections II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

The data demonstrate that residues for roxarsone and bacitracin were below their respective tolerances following a 5 day withdrawal period, thereby indicating an absence of interference.

Under §512(c)(2)(F)(ii) of the FFDCA, this approval for food producing animals does not qualify for marketing exclusivity beginning on the date of approval because the application does not contain reports of new clinical or field investigations (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant.

Attached labeling: Type C medicated Feed (Blue Bird)

Net weight lb (kg) on bag or bulk

Salinomycin/Bacitracin Methylene Disalicylate/Roxarsone – PNE Broiler Chicken Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 broiler chickens.

ACTIVE DRUG INGREDIENTS

Salinomycin……40 to 60 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 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.

WARNING: Withdraw 5 days before slaughter.

(OVER)

CAUTION: Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Any Town, USA 12345

Net weight lb (kg) on bag or bulk

Salinomycin/Bacitracin Methylene Disalicylate/Roxarsone – CNE Broiler Chicken Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 broiler chickens.

ACTIVE DRUG INGREDIENTS

Salinomycin……40 to 60 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 named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

DIRECTIONS FOR USE

Feed continuously for 5 to 7 days or as long as clinical signs persist, and then reduce bacitracin methylene disalicylate to prevention level (50 g/ton).

WARNING: Withdraw 5 days before slaughter.

(OVER)

CAUTION: Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Any Town, USA 12345

(OVER)

Net weight lb (kg) on bag or bulk

Salinomycin/Bacitracin Methylene Disalicylate/Roxarsone – PNE Roaster and Replacement (Breeder and Layer) Chicken Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 roaster and replacement (breeder and layer) chickens.

ACTIVE DRUG INGREDIENTS

Salinomycin……..……40 to 60 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 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. Discontinue use prior to sexual maturity.

WARNING: Withdraw 5 days before slaughter.

(OVER)

CAUTION: Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Any Town, USA 12345

(OVER)

Net weight lb (kg) on bag or bulk

Salinomycin/Bacitracin Methylene Disalicylate/Roxarsone – CNE Roaster and Replacement (Breeder and Layer) Chicken Ration

Type C Medicated Feed

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *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 roaster and replacement (breeder and layer) chickens.

ACTIVE DRUG INGREDIENTS

Salinomycin……..……40 to 60 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 named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

DIRECTIONS FOR USE

Feed continuously for 5 to 7 days or as long as clinical signs persist, and then reduce bacitracin methylene disalicylate to prevention level (50 g/ton). Discontinue use prior to sexual maturity.

WARNING: Withdraw 5 days before slaughter.

(OVER)

CAUTION: Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

MANUFACTURED BY

BLUE BIRD FEED MILL
Any Town, USA 12345

(OVER)