Approval Date:_____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-136

Salinomycin (BIO-COX®) plus Bacitracin Methylene Disalicylate (BMD®)

1) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*, and for increased rate of weight gain and improved feed efficiency in 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*, and as an aid in the <u>control</u> of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in broiler, roaster, and replacement (breeder and layer) chickens;

3) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*, and as an aid in the <u>prevention</u> of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in broiler, roaster, and replacement (breeder and layer) chickens.

Sponsored by:

Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

FREEDOM OF INFORMATION SUMMARY

Combined use of BIO-COX® and BMD® in Broiler, Roaster and Replacement Chicken Feeds

I. GENERAL INFORMATION

NADA: 141-136

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

Generic Names: Salinomycin
Bacitracin methylene disalicylate

Trade Names: BIO-COX®
BMD®

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*, and for increased rate of weight gain and improved feed efficiency in 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*, and as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp., or other organisms susceptible to bacitracin in broiler, roaster, and replacement (breeder and layer) chickens;

3) For the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*, and as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium* spp., or other organisms susceptible to bacitracin in broiler, roaster, and replacement (breeder and layer) chickens.

III. DOSAGE

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles, salinomycin as per 21 CFR 558.550(d)(3)(i) and bacitracin methylene disalicylate as per 21 CFR 558.76(d)(1)(i), (d)(1)(vi), and (d)(1)(ix). Salinomycin is supplied as a Type A medicated article in

concentrations of 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 activity per pound.

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

C. Recommended Dosage:

Salinomycin sodium	Salinomycin is added to broiler chicken feeds at concentrations from 40 to 60 grams/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 roaster and replacement chicken feeds at concentrations from 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency; 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; 3) 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.

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 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 chicken feeds for increased rate of weight gain and improved feed efficiency, and for use in broiler and replacement chicken feed as an aid in the prevention and control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR 558.76(d)(1)(i), (d)(1)(vi), and (d)(1)(ix), respectively). Effectiveness for each drug, salinomycin and bacitracin methylene disalicylate, when administered alone in accordance with its 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 NADA 46-592, respectively. Because salinomycin and bacitracin methylene disalicylate 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 provide appropriate concurrent use for the intended target population. The use of salinomycin plus bacitracin methylene disalicylate provides appropriate concurrent use because these drugs are intended to treat different conditions (salinomycin, coccidiosis; bacitracin methylene disalicylate, performance/necrotic enteritis) likely to occur simultaneously with sufficient frequency in broiler and replacement chickens. There is not 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 chickens for the purposes of Section 512(d)(4) of the FFDCA, as amended by the Animal Drug Availability Act of 1996, because salinomycin is approved only for prevention of a protozoan disease (coccidiosis) in broiler, roaster, and replacement chickens. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific effectiveness studies are required for the approval of NADA 141-136.

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 a 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 chicken feed for increased rate of weight gain and improved feed efficiency, and for use in broiler and replacement chicken feed 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)(i), (d)(1)(vi), and (d)(1)(ix), respectively). Target animal safety for each drug, salinomycin and bacitracin methylene disalicylate, when administered alone in accordance with its 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 NADA 46-592, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of salinomycin or bacitracin methylene disalicylate when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of this 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 141-136.

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

Data establishing the safety of salinomycin and bacitracin methylene disalicylate have been submitted to NADA 128-686 and NADA 46-592, 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.

B. Residue Data

The study entitled "Tissue levels in chickens fed salinomycin plus roxarsone plus bacitracin methylene disalicylate, 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 zero withdrawal period for broiler chickens fed salinomycin sodium (40 to 60 g/ton) and bacitracin methylene disalicylate (4 to 50 g/ton and 100 to 200 g/ton) and demonstrate that there is no assay interference among the 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.

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 (4 to 50 g/ton, 50 g/ton, and 100 to 200 g/ton) are safe and effective for the claims indicated in section II of this FOI Summary.

Results from residue studies support the assignment of a zero withdrawal period for broiler chickens fed salinomycin sodium (40 to 60 g/ton) and bacitracin methylene disalicylate (4 to 50 g/ton, 50 g/ton, or 100 to 200 g/ton), and demonstrate that there is no assay interference among the drugs.

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

Salinomycin/Bacitracin methylene disalicylate
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*, and for increased rate of weight gain and improved feed efficiency in roaster and replacement (breeder and layer) chickens.

ACTIVE DRUG INGREDIENT

Salinomycin……40 to 60 g/ton
Bacitracin methylene disalicylate ……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 Officials.

DIRECTIONS FOR USE

Feed continuously as sole ration. Discontinue use prior to sexual maturity.

CAUTION: For roaster and replacement (breeder and layer) chickens only. Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Salinomycin/Bacitracin methylene disalicylate
Broiler, 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*, and as an aid in the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin in broiler, roaster, and replacement (breeder and layer) chickens.

ACTIVE DRUG INGREDIENTS

Salinomycin……..……40 to 60 g/ton
Bacitracin methylene disalicylate……..……100 to 200 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

To control an outbreak of necrotic enteritis, start medication at first clinical signs of disease. The dosage range permitted provides for different levels based on severity of 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). Discontinue use prior to sexual maturity.

CAUTION: For broiler, roaster, and replacement (breeder and layer) chickens only. Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses.

MANUFACTURED BY
BLUE BIRD FEED MILL
Anytown, USA 12345

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ACTIVE DRUG INGREDIENTS

Salinomycin……..……40 to 60 g/ton
Bacitracin methylene disalicylate……..……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…….…….....……_____%

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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

Discontinue use prior to sexual maturity.

CAUTION: For broiler, roaster, and replacement (breeder and layer) chickens only. Do not feed to laying chickens. May be fatal if fed to adult turkeys or to horses.

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