Approval Date: July 3, 2000

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-155

Robenidine Hydrochloride (ROBENZ®) plus Bacitracin Methylene Disalicylate (BMD®) plus Roxarsone (3-NITRO®)

1. As an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*, 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.

2. As an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*, 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.

Sponsored by:

Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

FREEDOM OF INFORMATION SUMMARY

Combined use of ROBENZ®, BMD®, and 3-NITRO® in Broiler Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-155

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

Generic Names: Robenidine hydrochloride
Bacitracin methylene disalicylate
Roxarsone

Trade Names: ROBENZ®
BMD®
3-NITRO®

Marketing Status: OTC

II. INDICATIONS FOR USE:

1) As an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*, 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;

2) As an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*, 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.

III. DOSAGE:

A. Dosage form: This NADA provides for the combined use of these three Type A medicated articles, robenidine hydrochloride as per 21 CFR 558.515(d)(1)(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). Robenidine hydrochloride is supplied as a Type A medicated article in a single concentration of 30 grams robenidine 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. 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:

Robenidine hydrochloride	Robenidine is added to broiler chicken feed at concentration of 30 g/ton as an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*.
Bacitracin methylene disalicylate	1) Bacitracin methylene disalicylate is added to broiler 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 broiler 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.

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.

Robenidine hydrochloride, as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix* (21 CFR 558.515 (d)(1)(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, robenidine hydrochloride, bacitracin methylene disalicylate, and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADA 48-486 (to which Alpharma Inc. has a right of reference), and in Alpharma's approved NADAs 46-592, and 7-891, respectively.

Because robenidine hydrochloride, 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 robenidine hydrochloride plus bacitracin methylene disalicylate plus roxarsone provide appropriate concurrent use for the intended target population. The use of robenidine plus bacitracin methylene disalicylate plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (robenidine, coccidiosis; bacitracin methylene disalicylate, necrotic enteritis; roxarsone, pigmentation problems) likely to occur simultaneously with sufficient frequency in broiler 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. Robenidine hydrochloride 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 robenidine hydrochloride is approved only for prevention of a protozoal disease (coccidiosis) in broiler chickens. Roxarsone 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 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.

Robenidine hydrochloride, as provided by Roche Vitamins Inc., has previously been separately approved for use in broiler chickens as an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix* (21 CFR 558.515 (d)(1)(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, robenidine hydrochloride, bacitracin methylene disalicylate, and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADA 48-486 (to which Alpharma Inc. has a right of reference), and in Alpharma's approved NADAs 46-592, and 7-891, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of robenidine hydrochloride, 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 studies are required for approval of NADA 141-155.

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 robenidine hydrochloride, bacitracin methylene disalicylate, and roxarsone have been established by NADA 48-486, 46-592, and 7-891, respectively. Tolerances for residues of robenidine hydrochloride in chickens are established at 0.2 ppm in skin and fat and 0.1 ppm (negligible residue) in edible tissue other than skin and fat (21 CFR 556.580). 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

During experiment A-72-35-FT, male and female broiler chickens were fed medicated feed containing the combination of bacitracin methylene disalicylate at 200 g/ton, robenidine hydrochloride at 30 g/ton and roxarsone at 45 g/ton for 8 weeks. Tissues were collected on 0 and 1 day withdrawal of medication for bacitracin assay, and at 0, 3 and 5 days withdrawal for robenidine and roxarsone analyses. There were no positive findings for bacitracin in any of the tissues (fat, kidney, liver, muscle, and skin) taken at 0 and 1 day withdrawal. Residues of robenidine at 0 day withdrawal of medication averaged < 0.20, 0.32, 0.29 and 0.24 ppm for muscle liver, kidney, and skin, respectively. Arsenic levels in tissues of medicated birds at 0 day withdrawal averaged 1.17, 0.85, 0.08, 0.12, and 0.18 ppm for liver, kidney, fat, skin, and muscle, respectively. Arsenic analysis at 3 days withdrawal of medication shows residues below the established tolerances.

The available residue chemistry information supports the assignment of a five day withdrawal period for broiler chickens fed the combination of robenidine hydrochloride (30 g/ton), bacitracin methylene disalicylate (50 or 100 to 200 g/ton), and roxarsone (22.7 to 45.4 g/ton).

C. Regulatory Methods for Residues

The regulatory analytical method for robenidine hydrochloride is the polarographic method on file at the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

A microbiological method is used to assay 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, 7500 Standish Place, Rockville, MD 20855.

A spectrophotometric method is used to assay tissues for bacitracin 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 use of robenidine hydrochloride (30 g/ton) plus bacitracin methylene disalicylate (50 g/ton and 100 to 200 g/ton) plus roxarsone (22.7 to 45.4 g/ton) with a 5 day withdrawal period is 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

Robenidine hydrochloride/Bacitracin methylene disalicylate/Roxarsone Broiler Chicken Ration

Type C Medicated Feed

As an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*, 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 INGREDIENT

Robenidine hydrochloride……30 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 prior to slaughter.

(OVER)

CAUTION: For broiler chickens only. Do not feed to laying chickens. 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

Robenidine hydrochloride/Bacitracin methylene disalicylate/Roxarsone Broiler Chicken Ration

Type C Medicated Feed

As an aid in the prevention of coccidiosis caused by *Eimeria mivati, E. brunetti, E. tenella, E. acervulina, E. maxima,* and *E. necatrix*, 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 INGREDIENT

Robenidine hydrochloride……30 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

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).

WARNING: Withdraw 5 days prior to slaughter.

(OVER)

CAUTION: For broiler chickens only. Do not feed to laying chickens. 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