

Approval Date: FEB 12 2001

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-156

**Amprolium (AMPROL[®]) plus
Bacitracin Methylene Disalicylate (BMD[®])**

For the development of active immunity to coccidiosis, and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Sponsored by:

**Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024**

FREEDOM OF INFORMATION SUMMARY

Combined use of AMPROL[®] and BMD[®] in Replacement Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-156

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

Generic Names: Amprolium
Bacitracin methylene disalicylate

Trade Names: AMPROL[®]
BMD[®]

Marketing Status: OTC

II. INDICATIONS FOR USE:

For the development of active immunity to coccidiosis, and for increased rate of weight gain and improved feed efficiency in replacement chickens.

III. DOSAGE:

- A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles, amprolium as per 21 CFR 558.55(d)(2)(i) and bacitracin methylene disalicylate as per 21 CFR 558.76(d)(1)(i). Amprolium is supplied as a Type A medicated article in a single concentration of 25 percent amprolium. Bacitracin methylene disalicylate is supplied as a Type A medicated article in concentrations of 10, 25, 30, 40, 50, 60, and 75 grams bacitracin activity per pound.
- B. Route of Administration: Oral, *via* the feed.
- C. Recommended Dosage:
Amprolium Amprolium is added to replacement chicken feed at concentrations of 36.3 to 113.5 g/ton for development of active immunity to coccidiosis.

Bacitracin methylene disalicylate Bacitracin methylene disalicylate is added to chicken feed at concentrations from 4 to 50 g/ton for increased rate of weight gain and improved feed efficiency.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

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.

Amprolium, as provided by Merial, has previously been separately approved for use in replacement chickens for the development of active immunity to coccidiosis (21 CFR 558.55(d)(2)(i)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for increased rate of weight gain and improved feed efficiency in chickens (21 CFR 558.76(d)(1)(i)). Effectiveness for each drug, amprolium and bacitracin methylene disalicylate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 12-350 (to which Alpharma Inc. has a right of reference) and NADA 46-592, respectively.

Because amprolium 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 amprolium plus bacitracin methylene disalicylate provide appropriate concurrent use for the intended target population. The use of amprolium plus bacitracin methylene disalicylate provide appropriate concurrent use because these drugs are intended to treat different conditions (amprolium, coccidiosis; bacitracin methylene disalicylate, weight gain and feed efficiency) likely to occur simultaneously with sufficient frequency in replacement 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. Amprolium 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 amprolium is approved only for prevention of a protozoal disease (coccidiosis) in replacement chickens and it is not approved for use in chickens for the diagnosis, cure, mitigation, treatment or prevention of bacterial disease.

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.

Amprolium, as provided by Merial, has previously been separately approved for use in replacement chickens for the development of active immunity to coccidiosis (21 CFR 558.55(d)(2)(i)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for increased rate of weight gain and improved feed efficiency in chickens (21 CFR 558.76(d)(1)(i)). Target animal safety for each drug, amprolium and bacitracin methylene disalicylate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 12-350 (to which Alpharma Inc. has a right of reference) and 46-592, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of amprolium 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 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 141-156.

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 bacitracin methylene disalicylate and amprolium have been established by NADA 46-592 and 12-350, respectively. Tolerances for residues for bacitracin in uncooked edible tissues and eggs of chickens are established at 0.5 ppm (0.02 unit/g) in 21 CFR 556.70. Tolerances for residues of amprolium (1-(4-amino-2-n-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride) are established at 1 ppm in uncooked liver and kidney, 0.5 ppm in uncooked muscle, 8 ppm in egg yolks, and 4 ppm in whole eggs (21 CFR 556.50).

B. Residue Data

The safety of edible tissues from chickens fed feed with amprolium and bacitracin methylene disalicylate was established in Merial's NADA 36-304 [AMPROL HI-E[®] (amprolium/ethopabate/BMD)].

Approval of this NADA for the use of amprolium (36.3 to 113.5 g/ton) and bacitracin methylene disalicylate (4 to 50 g/ton) in replacement chickens will not increase the risk of human exposure to these residues since the combination of amprolium (36.3 to 113.5 g/ton) and bacitracin methylene disalicylate (100 to 200 g/ton) is currently approved for use in replacement chickens (21 CFR 558.58(d)(1)(i)). The combination of amprolium (113.5 to 227 g/ton) and bacitracin methylene disalicylate (4 to 50 and 100 to 200 g/ton) is also currently approved for use in broiler and replacement chickens (21 CFR 558.58(d)(1)(iv)).

The available residue chemistry information supports the assignment of a zero day withdrawal period for replacement chickens fed the combination of bacitracin methylene disalicylate (4 to 50 g/ton), and amprolium (36.3 to 113.5%).

C. Regulatory Methods for Residues

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 (Room 1061), 5600 Fishers Lane, Rockville, MD 20852.

A regulatory analytical method is used to assay for detection of residues of amprolium is a fluorometric test. A description of the regulatory method is filed in the *Food Additives Analytical Manual* which is on display in the Food and Drug Administration's Freedom of Information Publication Room (Room 1061), 5600 Fishers Lane, Rockville, MD 20852.

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 bacitracin methylene disalicylate (4 to 50 g/ton) plus amprolium (36.3 to 113.5 g/ton) with a zero 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.

Because higher levels of the drugs used in this combination are currently being used in combination, this combination does not pose an increased risk to human food safety and the zero day withdrawal period is adequate.

Attached labeling: Type C Medicated Feed (Blue Bird) – Replacement chickens

Net weight lb (kg) on bag or bulk
Amprolium-SV1/Bacitracin methylene disalicylate
Replacement Chicken Ration
Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....113.5 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.....%
Salt¹, not less than.....%
Salt¹, not more than.....%
Sodium², not less than.....%
Sodium², not more than.....%

¹If added.

²Shall 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 sole ration under conditions of severe exposure to coccidiosis up to 5 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-SV2/Bacitracin methylene disalicylate
Replacement Chicken Ration
Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....72.6 to 113.5 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..... %
Salt¹, not less than..... %
Salt¹, not more than..... %
Sodium², not less than..... %
Sodium², not more than..... %

¹If added.

²Shall 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 sole ration under conditions of severe exposure to coccidiosis from 5 to 8 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-SV3/Bacitracin methylene disalicylate Replacement Chicken Ration Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....	36.3 to 113.5 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.....	_____ %

¹If added.

²Shall 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 sole ration under conditions of severe exposure to coccidiosis over 8 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk
Amprolium-M1/Bacitracin methylene disalicylate
Replacement Chicken Ration
Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....72.6 to 113.5 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..... %
Salt¹, not less than..... %
Salt¹, not more than..... %
Sodium², not less than..... %
Sodium², not more than..... %

¹If added.

²Shall 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 sole ration under conditions of moderate exposure to coccidiosis up to 5 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-M2/Bacitracin methylene disalicylate Replacement Chicken Ration Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....	54.5 to 113.5 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.....	_____ %

¹If added.

²Shall 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 sole ration under conditions of moderate exposure to coccidiosis from 5 to 8 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-M3/Bacitracin methylene disalicylate Replacement Chicken Ration Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....	36.3 to 113.5 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.....	_____ %

¹If added.

²Shall 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 sole ration under conditions of moderate exposure to coccidiosis over 8 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-S1/Bacitracin methylene disalicylate Replacement Chicken Ration Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....	36.3 to 113.5 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.....	_____ %

¹If added.

²Shall 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 sole ration under conditions of slight exposure to coccidiosis up to 5 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-S2/Bacitracin methylene disalicylate Replacement Chicken Ration Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....	36.3 to 113.5 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.....	_____ %

¹If added.

²Shall 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 sole ration under conditions of slight exposure to coccidiosis from 5 to 8 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

MANUFACTURED BY

BLUE BIRD FEED MILL
Anytown, USA 12345

Net weight lb (kg) on bag or bulk

Amprolium-S3/Bacitracin methylene disalicylate Replacement Chicken Ration Type C Medicated Feed

For the development of active immunity to coccidiosis and for increased rate of weight gain and improved feed efficiency in replacement chickens.

Active Drug Ingredient

Amprolium.....	36.3 to 113.5 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.....	_____ %

¹If added.

²Shall 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 sole ration under conditions of slight exposure to coccidiosis over 8 weeks of age.

CAUTION: For replacement chickens only. Do not use in feeds containing bentonite.

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BLUE BIRD FEED MILL
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