

AUG 13 1998

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-937

COBAN[®] + BMD[®] (monensin sodium + bacitracin methylene disalicylate) for
Growing Turkeys

“... for the prevention of coccidiosis caused by *Eimeria adenoeides*, *E. meleagrimitis*, and
E. gallopavonis and as an aid in the control of transmissible enteritis complicated by organisms
susceptible to **bacitracin methylene disalicylate** in growing turkeys.”

Sponsored by

ELANCO ANIMAL HEALTH **Co.**

Date of Approval:

I. GENERAL INFORMATION

NADA Number: **140-937**

Sponsor: Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Established Name: monensin sodium and bacitracin methylene disalicylate

Trade Name: COBAN[®] + BMD[®]

Marketing Status: over-the-counter

Pharmaceutical Classification: anticoccidial (polyether ionophore)

Classification: antibacterial agent and/or growth promotant (polypeptide antibiotic)

Effect of Supplement: This supplemental application provides for a new combination including bacitracin methylene disalicylate, as an aid in the control of transmissible enteritis complicated by susceptible organisms in growing turkeys at a new use level, 200 grams per ton, when used in Type C medicated feed in combination with monensin sodium at 54 to 90 grams per ton for the prevention of coccidiosis.

II. INDICATIONS FOR USE

For the prevention of coccidiosis caused by *Eimeria adenoeides*, *E. meleagrimitis*, and *E. gallopavonis* and as an aid in the control of transmissible enteritis complicated by organisms susceptible to bacitracin methylene disalicylate in growing turkeys.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. Dosage Form: Intended use is for Type C medicated feed. Bacitracin methylene disalicylate is supplied as a Type A Medicated Article in concentrations of 25,30,40, 50, 60, or 75 grams of bacitracin activity per pound. Monensin sodium is supplied as a Type A Medicated Article in concentrations of 45 and 60 grams of monensin activity per pound.

B. Route of Administration: COBAN[®] + BMD[®] should be administered orally ad libitum, via feed.

C. Approved Dose: The approved dosage of bacitracin methylene disalicylate is 200 grams per ton in combination with 54 to 90 grams per ton of monensin sodium in Type C medicated feeds fed continuously as the sole ration to growing turkeys. The optimum level of monensin depends upon the severity of coccidiosis.

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/drug** intended only for the same use as another active **ingredient/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 nontropical antibacterial active **ingredient/animal drug**, there is substantial evidence that each of the nontropical antibacterial active **ingredients/animal drugs** makes a contribution to the labeled effectiveness [Section 512(d)(4)(D) of the FFDCA].

The approval of NADA 46-592 established the effectiveness of **bacitracin methylene disalicylate** (200 g/ton) as an aid in the control of transmissible enteritis complicated by susceptible organisms in growing turkeys when used for 5 to 7 days or as long as symptoms persist.

The approval of NADA 130-736 established the effectiveness of monensin sodium (54 to 90 g/ton) for the prevention of coccidiosis in **growing** turkeys due to *Eimeria adenoeides*, *E. meleagritidis*, and *E. gallopavonis*.

The original approval of NADA 140-937 established the effectiveness of **bacitracin methylene disalicylate** (4 to 50 g/ton) for increased rate of weight gain in combination with monensin sodium (54 to 90 g/ton) for the prevention of coccidiosis caused by *Eimeria adenoeides*, *E. meleagritidis*, and *E. gallopavonis* in growing turkeys. The data in this approval further demonstrates that the addition of **bacitracin methylene disalicylate** (220 g/ton) to monensin sodium (60 g/ton) in complete turkey feed had no adverse effects on **anticoccidial** efficacy.

Based on the data in the approved single ingredient applications, the original approval of this NADA, and the provisions of the Animal Drug Availability Act of 1996, the burden to establish effectiveness of the combination use has been met.

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 animal drugs/active ingredients 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 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 animal drug is **safe** for the target animal.

The basic animal safety data for the individual drugs may be found in NADA 46-592 for **BMD®** and in NADA 130-736 for **COBAN®**. The effectiveness data in the original approval of this NADA demonstrate that no ill effects occurred when the drugs were combined, indicating that they are safe when fed in combination.

Additional safety studies were not required because: (1) the drugs have been approved singularly, and (2) adequate documentation has been provided to show that these compounds are compatible in combination when used in turkey feeds. Therefore, based on data in the original NADAs for the single ingredients, it is concluded that this combination of drugs maybe safely fed to growing turkeys.

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 target animal 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. Toxicity Tests: Basic toxicity data for **bacitracin methylene disalicylate** may be found in NADA 46-592 (41 FR 10793; March 15, 1976 and 46 FR 41041; August 14, 1981), sponsored by ALPHARMA, Inc. Basic toxicity data for **monensin** may be found in NADA 38-878 (35 FR 7734; May 20, 1970), sponsored by **Elanco Animal Health**. Specific data for monensin in turkeys is included in NADA 130-736 (52 FR 1571 8; April 30, 1987).

B. Tolerances and Safe Concentrations of Residues: The tolerance for residues of **bacitracin methylene disalicylate (BMD®)** in uncooked edible tissues is established at

21 CFR 556.70 at 0.5 ppm, negligible residue. A tolerance for marker residues of monensin (COBAN[®]) in turkeys is not needed (21 CFR 556.420).

- c. Tissue Residue Depletion Studies: In a tissue residue study conducted to support the approval of the original NADA, five male and five female turkeys were medicated with monensin (90 g/ton) and **bacitracin methylene disalicylate** (200 g/ton) for 27 days and slaughtered at zero withdrawal (6 hours). The tissues were assayed for monensin (skin fat) and **bacitracin methylene disalicylate** (muscle). All tissues sampled had less than 0.04 ppm of monensin and less than 0.3 ppm of **bacitracin methylene disalicylate**, which are the respective limits of detection for these assays. These results are comparable to those obtained when each drug is administered alone; therefore, these data support a zero withdrawal period for human consumption of edible tissues of turkeys treated with **bacitracin methylene disalicylate** plus **monensin** in the feed.
- D. Assay Non-Interference Study: Data from tissue assays, which were included in the original approval of this NADA, demonstrated that there is no interference by monensin for **bacitracin methylene disalicylate** and no interference by **bacitracin methylene disalicylate** for monensin.
- E. Regulatory Methods:
1. **Bacitracin:** Antibiotic Residue in Milk, Dairy Products, and Animal Tissues: Methods, Reports, Protocols. National Center for Antibiotic and Insulin Analyses, Dept. HEW, Washington, DC 20204; Rev. October 1968.

Modified Method for Determination of Bacitracin in Tissue, Test Procedure Code 9A. A.L. Laboratories Inc., One Executive Drive, P.O. Box 1399, Fort Lee, NJ 07024.
 2. **Monensin:** Determination of Monensin in Tissues and Eggs. Method 5801654. Eli Lilly and Company, Box 708, Greenfield, IN 46140.

These methods are on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

VII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that monensin (54 to 90 g/ton) plus **bacitracin methylene disalicylate** (200 g/ton) are safe and effective for the prevention of coccidiosis caused by *Eimeria adenoides*, *E. meleagritidis*, and *E. gallopavonis* and as an aid in the control of transmissible enteritis complicated by organisms susceptible to **bacitracin methylene disalicylate** in growing turkeys.

In accordance with 21 CFR 514.106(b)(2)(iii) & (v), this supplemental approval is a Category H change which did not require a reevaluation of safety and efficacy data in the parent applications.

Residue data show that monensin is well within the established safe concentrations of 4.5 ppm in liver, 3.0 ppm skin/fat, and 1.5 ppm muscle of the turkey at zero withdrawal. Residue data show bacitracin methylene disalicylate is well below tolerance of 0.5 ppm in edible turkey tissues at zero withdrawal.

In accordance with 21 CFR 25.33(a)(2), the Agency has **carefully** considered the potential environmental effects of this action and has concluded that the action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment.

APPENDIX I: APPROVED LABELING: Facsimile bluebird labeling is provided.

Lot Number_____

BLUE BIRD TURKEY FEED

TYPE C MEDICATED FEED

For the prevention of coccidiosis caused by *E. adenoides*, *E. meleagrimitis* and *E. gallopavonis*, and as an aid in the control of transmissible enteritis in growing turkeys complicated by organisms susceptible to bacitracin methylene disalicylate.

ACTIVE INGREDIENT

Monensin (as monensin sodium)54 to 90 g/ton
Bacitracin Methylene Disalicylate200 g/ton

GUARANTEED ANALYSIS

Crude protein, not less than%
Crude fat, not less than%
Crude fiber, not more than%

INGREDIENTS

Each ingredient must be specifically named (unless stated as such in the guaranteed analysis listing) in accordance with the names and definitions listed in Tide 21 CFR 501.110.

DIRECTIONS FOR USE

Feeding Directions: Feed continuously as the sole ration. The optimum level depends upon the severity of coccidiosis.

CAUTION: Do not allow horses, other equines, mature turkeys or guinea fowl access to feed containing monensin. Ingestion of monensin by horses and guinea fowl has been fatal. Some strains of turkey coccidia may be monensin tolerant or resistant. Monensin may interfere with development of immunity to turkey coccidiosis.

Store in a cool, dry place,

NET WEIGHT ON BAG OR BULK

Blue Bird Feed Mill
Robin, IN 12345